Summary, Answers and Comments by the Medical Products Agency, Sweden, on the Concept Paper for Public Consultation, published by the European Commission, Health and Consumers Directorate-General, Public Health and Risk Assessment, Pharmaceuticals

Consultation item	MPA Answer	Comment/reason
1	Yes	Comment provided as requested
2	Yes	No comment provided
3	Yes	Comment provided as requested
4	Yes	No comment requested
5	Yes	No comment requested
6	Third alternative, “referral for decision at EU level”	Reasons provided as requested
7	Second alternative, “CAP is mandatory for all multinational clinical trials”	Reasons provided as requested
8	Yes	Comment provided as requested
9	Yes	Comment provided as requested
10	Yes	No comment provided
11	Yes	No comment provided
12	Other key aspects for which detailed rules are needed: safety of clinical trial participants	Comment provided as requested
13	Yes	Comment provided as requested
14	Not within the remit of MPA	No comment provided
15	Yes	Comment provided as requested
16	Yes	Comment provided as requested
17	Yes	No comment provided
18	No appraisal requested	Comment provided as requested

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Contents

1. Cooperation in Assessing and Following Up Applications for Clinical Trials

1.1. Single submission with separate assessment

One option would be for the sponsor to send the necessary documentation to all Member States concerned through a single 'EU portal' ('single submission'), administered by the European Medicines Agency ('the Agency'). The 'EU portal' would subsequently distribute the information to the Member States concerned. Subsequent applications by the same sponsor (or, in certain cases, other sponsors) for authorisation of a clinical trial could simply refer to information previously submitted to the EU portal.
Subsequent applications by the same sponsor (or, in certain cases, other sponsors) for authorisation of a clinical trial could simply refer to information previously submitted to the EU portal.

Preliminary appraisal: A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned.

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

MPA Answer: Yes.

***MPA Comment*: The view that all Clinical Trial Applications (CTAs) should go through a common 'EU portal' is supported. Preferably, these CTAs should be forwarded to the concerned Member States without requiring further processing, such as validation or payment for the procedure.**

Regarding the *assessment* of the information, this assessment would be done independently by each Member State, as at present.

Preliminary appraisal: A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain.

Consultation item 2: Do you agree with this appraisal? Please comment.

MPA Answer: Yes.

No comments are provided by MPA

1.2. Single submission with subsequent central assessment

This option would be a single submission (see above), after which the submitted information would be centrally assessed by a scientific committee made up of representatives of all the Member States. This option, would be similar to the 'centralised marketing authorisation' for medicinal products.

Preliminary appraisal: A central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for the following reasons:

- This option would insufficiently take account of ethical, national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case.
- The sheer number of multinational clinical trials per year (approx. 1200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials.
- The involvement of all Member State is not needed, as very few clinical trials are rolled out in more than five or six Member States.

Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researchers.

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

MPA Answer:Yes.

***MPA Comment*: Besides the disadvantages mentioned above, it would be difficult to compose such a Central Scientific Committee for assessments, in particular deciding:**

- **if all Member States should be represented or not in the Committee**
- **if all Committee Members should have voting rights, i.e. also Member States that are not concerned by the Clinical Trial**

A Central Scientific Committee for assessments would lead to the development of different standards for multinational and national trials.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

This option would be a single submission (see above), which would be followed by a 'coordinated assessment procedure' (CAP). The CAP would be modelled, in some respects, on the decentralised procedure for marketing authorisations, while having a stronger element of joint assessment by the Member States concerned.
The CAP would:

- allow all Member States concerned to input to the assessment of the application for a clinical trial regarding the aspects set out below (see point 1.3.1);
- provide for a 'Reporting Member State' whose role would be to lead the assessment of the application for a clinical trial;
- involve only the Member States concerned with a limited role for the Commission or the Agency – the latter acting as secretariat
- only address certain aspects of the assessment of an application for a clinical trial (see point 1.3.1);
- lead to a 'single decision' per Member State which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment (see point 1.3.1).

The CAP would apply to the initial authorisation of a clinical trial, as well as subsequent 'substantial amendments'.
Under the CAP, it would be up to each Member State to divide the tasks between the competent national authority and the

Ethics Committee.

Preliminary appraisal: The CAP could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of Member States.
Regarding the CAP, four issues need to be considered in particular and shall be discussed in this concept paper:

- Scope of the CAP (point 1.3.1);
- Disagreement with assessment report (point 1.3.2);
- Mandatory/optional use (point 1.3.3);
- Timelines (point 1.3.4).

1.3.1. Scope of the CAP

Not all aspects considered in a clinical trial application are suitable for an assessment in the CAP. In particular, ethical issues clearly fall within the ambit of Member States and should remain there.
To establish the scope of the CAP one has to have clarity of the three areas which are considered in a clinical trials application:
a) The risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling. This includes the following:

- Acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects (including control groups), taking account of
  - the characteristics of and knowledge about the investigational medicinal product,
  - the characteristics of the intervention compared to normal clinical practice;
  - the design of the trial;
  - the relevance of the trial, including the credibility of the results;
- compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;
- compliance with the requirements for labelling of the medicinal products intended for the clinical trial;
- completeness and adequateness of the investigator's brochure.

b) Ethical aspects related to informed consent, recruitment and reward. This includes the following:

- completeness and adequateness of the information submitted to obtain informed consent;
- arrangements for rewarding and compensation of investigators and trial subjects;
- arrangements for the recruitment of trial subjects.

c) Local aspects related to suitability of sites, the investigator, and national rules. This includes the following:

- suitability of the investigator;
- suitability of the clinical trials site;
- adequateness and completeness of the insurance or indemnisation covering the investigator and sponsor;
- compliance with the applicable rules on personal data protection.

Only the aspect under point a) would be suitable for the CAP. In particular, the aspects under b) and c) are not suitable for the CAP as they relate to ethical issues (as is the case for b) or to local expertise (as is the case for c).

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

MPA Answers: Yes

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

MPA Answers: Yes

1.3.2. Disagreement with the assessment report

Disagreements amongst Member States about the assessment done under the CAP (ie the aspects listed in point 1.3.1.a) could be resolved in the following ways:

- an individual Member State could be allowed an ‘opt out’, if justified on the basis of a ‘serious risk to public health or safety of the participant’;
- the Member States concerned could vote on the issue and decide by simple majority; or
- the matter could be referred to the Commission or the Agency for a decision at EU level.

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

MPA Answer: The third alternative, "referral for decision at EU level"

***MPA Comment*: Only a referral will ensure that CAP will reach a common decision at EU level. The voting procedure is not recommended for these issues. Competence and expert views are at risk of being diluted by the majority votes from non-experts. Experts from all concerned Member States are likely to assess the trial from different angles.**

1.3.3. Mandatory/optional use

As to whether the CAP should be mandatory or optional, three possibilities could be considered:

- CAP is **mandatory for all** clinical trials. (This would mean that the provisions on authorisation in the Clinical Trials Directive would be replaced);
- CAP is **mandatory for all multinational** clinical trials. (This would mean that the provisions on authorisation in the Clinical Trials Directive would be maintained only for single-country clinical trials); or
- CAP is **optional**. (This would mean that sponsors could continue to refer to the national procedures laid down in the Clinical Trials Directive).

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

MPA Answer: The second alternative, "CAP is mandatory for all multinational clinical trials".

***MPA Comment*: A CAP mandatory to all multinational clinical trials is preferred. The Commission should consider how to deal with a situation where a sponsor submits a Clinical Trial Application (CTAs) in one Member State, and later wants to expand the trial to more Member States.**

1.3.4. Tacit approval and timelines

As a general rule the Clinical Trials Directive provides for a tacit approval by the national competent authority if, within 60 days, no grounds for non-acceptance have been raised.
In practice, a tacit approval is the exception. Moreover, this rule does not apply to Ethics Committees.
To take account of this, the CAP could be based on the concept of an obligatory single authorisation per Member State prior to commencement of the clinical trial. Under the CAP, a 'tacit approval' would not be possible.
Regarding timelines of the CAP, these should not be longer than the timelines provided today in the Clinical Trials Directive (i.e. as a general rule 60 days). There should be clear rules on the timelines for the approval of substantial amendments, taking into account that the assessment is limited to the aspects of the clinical trial which have been subject to a substantial amendment.
Moreover, the timelines could be shortened where the risk to trial subjects is low and where the assessment in the CAP is limited largely to issues of reliability of data. To this end, these types of trials (hereinafter 'type-A trials') could be identified in a pre-assessment.

A type A trial could be defined as '*a clinical trial which, on the basis of the following criteria, poses only minimal risks to the safety of the trial subject compared to normal clinical practice:*
(*a) The safety profile of all investigational medicinal products used in the trial is sufficiently known. This shall be the case if the investigational medicinal products used in the trial are:*

- *either authorised in a Member State concerned in accordance with Directive 2001/83/EC or Regulation 726/2004, and used within the authorised indication;*
- *part of a standard treatment in a Member State concerned.*

(b) The interventions in the trial do not pose more than insignificant additional risk to the safety of the trial subject compared to normal clinical practice in a Member State concerned.'

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

MPA Answer: Yes

***MPA Comment*: Concerning *pre-assessment of low risk trials (Type A*) and shorter timelines for these, several issues must be resolved, e.g.:**

- **The pre-assessment should preferably be done by the Concerned Member States**
- **A faster procedure for Type A trials would preferably forward all justified Grounds for Non-Acceptance (GNAs) from Concerned Member States to the Sponsor, avoiding duplicates. Editing/deleting GNAs would require more coordination time between Concerned Member States.**

Further comments on the proposed Type A trials:

- **Preferably, the first point above under a) should not only apply to Investigational Medicinal Products (IMPs) authorised in the Concerned Member State, but also IMPs authorised in other Member States for the same indication as proposed in the trial.**
- **The second point under a), "part of a standard treatment" is not adequate. Standard clinical practise varies between Member States and other Member States or the EMA cannot evaluate this aspect correctly. Standard treatments outside approved indications within EU should not be applicable for Type A trials, why this point should preferably deleted from the definition above.**

2. Better Adaptation to Practical Requirements and a More Harmonised, Risk-Adapted Approach to the Procedural Aspects of Clinical Trials.

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of 'non-interventional' trials

The definition of a 'non-interventional trial' (Article 2(c) of the Clinical Trials Directive) could be broadened, thereby excluding more studies from the scope of the Clinical Trials Directive (Article 1(1)).
At present, a 'non-interventional trial' is defined very narrowly. Three criteria have to be met simultaneously: the medicine is used within the terms of the marketing authorisation; there is no protocol and no additional intervention.
While some aspects of certain types of non-interventional trials have recently been harmonised at EU level,other aspects, as well as certain other non-interventional trials are still regulated at national level. Therefore, in some respects the rules for non-interventional trials may be in some Member States more lenient compared to those for clinical trials.
One may therefore argue that broadening the definition of a 'noninterventional trial' would limit the impact of the Clinical Trials Directive.
However, excluding trials from the scope of the Directive would also undermine past and future efforts to harmonise them to the extent that responsibility for regulating them would revert to the Member States. This would introduce differences in trial subject protection in the EU. Moreover, it would make conduct of these studies in the EU more cumbersome.

Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive. See in particular points 2.2 to 2.5.

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

MPA Answer: Yes

***MPA Comment*: The Concept of Type A trials mentioned under 1.3.4 would be a solution to low-intervention trials.**

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

It is not desirable to exempt 'academic/non-commercial sponsors' *as such* from regulatory requirements: It is difficult to see why rules designed to protect the safety and rights of participants and the reliability and robustness of data should apply to some types of sponsor and not to others. Besides, it is difficult in practice to establish whether a sponsor is acting in a 'non-commercial' or a 'commercial' context. The commercial use of clinical trial data may be indirect, or may become apparent only after a clinical trial has ended. A number of other arguments in support of this view were put forward during the 2009/10 public consultation and listed in the summary of responses.
Moreover, if clinical trials by 'academic/non-commercial sponsors' were excluded from the scope of the Clinical Trials Directive, they would not be subject to harmonised rules at EU level. Member States would again be responsible for regulating these trials via national laws. This would introduce differences in trial subject protection in the EU. Moreover, it would make conduct of these studies in the EU more cumbersome, which is not in the interest of 'academic/noncommercial sponsors' performing clinical trials in different Member States.

Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial'). See in particular points

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

MPA Answer: Yes

No comments are provided by MPA

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Often cited as examples for the need for greater harmonisation and riskadaptation in the European Union are the rules on

- the content of the clinical trials application dossier, and
- safety reporting.

To address this need, sufficiently detailed provisions on these topics could be included in Annexes to the basic legal act. The Commission could, when necessary, update them by means of delegated acts. In drawing up these Annexes, one would have to take into account:

- the risk to trial subject safety compared to normal clinical practice;
- the risk to data reliability and robustness;
- international harmonisation work, such as the guidelines of the International Conference on Harmonisation ('ICH').
- The contents of the Annexes would build on work recently carried out by the Commission, in particular the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial* (CT-1), as well as parts of the *Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use* (CT-2), and the *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use* (CT-3), which is currently under review.

Preliminary appraisal: This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.

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

MPA Answer: Yes

No comments are provided by MPA

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

MPA Answer: Yes

***MPA Comment:* A new legislation should support the use of EudraVigilance for the monitoring of safety of clinical trial participants. Therefore not only Suspected Unexpected, Serious adverse reactions (SUSARs) but also Serious Adverse Reactions (SARs) should be reported to EudraVigilance in accordance with the reporting requirements for expedited reporting and development safety updates reports (DSURs).**

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Medicinal products intended for research and development trials are excluded from the rules for medicinal products as set out in Directive 2001/83/EC (Article 3(3) of Directive 2001/83/EC).

Some of these products fall within the definition of a 'investigational medicinal product' ('IMP') as defined in the Clinical Trials Directive (Article 2(c)). For these products, an extensive set of rules covers manufacturing, labelling, and even costs. These rules are often perceived as not risk-adapted and too onerous.

In practice, apart from IMPs a clinical trial involves often products which fall within the exemption of Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMP. Examples are medicinal products used as challenge agents, rescue medication, and background treatment. These medicinal products, which are often referred to as 'non-IMPs', are not specifically regulated in the Clinical Trials Directive.

In practice, the legal uncertainties surrounding these aspects, and the diverging approaches in Member States, create major difficulties when performing multinational clinical trials. To address this, the following cumulative approach could be pursued:

- The definition of IMP could be changed and clarified by narrowing it as follows: '*A medicinal product which falls within the definition of Article 3(3) of Directive 2001/83/EC, and which is being tested or used as reference in a clinical trial.*' This would ensure that only the medicines that are the object of the study are covered by the requirements for IMP;
- The notion of 'auxiliary medicinal product', covering all other medicinal products used in the context of the clinical trial, could be introduced: *'A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC which is not an investigational medicinal product';*
- 'Auxiliary medicinal products' could be subjected to a proportionate regulatory regime, which would be separate from IMPs; and
- The rules for dossier requirements, reporting, and labelling for both IMPs and auxiliary medicinal products could be set out in the Annex to the basic legal act (see point 2.2).
-

Preliminary appraisal: This combined approach would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.

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

MPA Answer: Yes

***MPA Comment:* As to the definition of IMP, the proposed definition is clear. The rational for introducing the term auxiliary medicinal products instead of the recently**

defined term non-investigational medicinal products (NIMPs) needs further clarification.
The rules for dossier requirements, reporting and labelling of IMPs and NIMPs/auxiliary medicinal products should preferably be included in the clinical trial directive. In contrast, the idea of placing these rules in an Annex is considered impractical and inconvenient.

2.4. Insurance/indemnisation

Several policy options are proposed in the concept paper (not presented here in full), such as:

- Removing insurance/indemnisation requirements for low-risk trials: This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects (see point 1.3.4); or
- Optional indemnisation by Member State: This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today (see annex), the burden on national budgets would be minimal.

Preliminary appraisal: Both policy options could be a viable solution.

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

MPA Answer: This issue is not within the remit of the MPA.

2.5. Single sponsor

The Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the Ethics Committee.
It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous.
Two options could be considered:

- Option 1: maintaining a 'single sponsor'
- Option 2: allowing for a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', where each sponsor is 'responsible' for a specific task or for the conduct of the trial in a Member State.

When assessing the possibility of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', one has to bear in mind some important points:

- The responses to the 2009/10 public consultation show that the concept of 'responsibility' for the trial is often confused with 'liability' vis-à-vis the trial subject in case of damages. The latter, however, is a matter of civil/common law regarding contractual or extra-contractual obligations in the Member State concerned. When establishing the liability of a person or persons, the national rules for contractual and extra-contractual obligations apply. This issue is independent of the notion of 'sponsor' in the sense of 'responsibility vis-à-vis the national competent authority and the Ethics Committee'. Therefore, a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship' would not allow an actor to evade liability in terms of civil/common law.
- Regarding the 'responsibility' of the sponsor, the main problem seems to stem from the divergent requirements amongst Member States for conducting clinical trials. If these requirements were truly harmonised (see point 2.2), the question of the 'responsibility' for a clinical trial may be less critical.
- No matter which of the above options is pursued, there has to be a person who can ultimately and authoritatively inform the national competent authority about the clinical trial, in particular in the case of multinational trials. Examples are information about status of a trial or about adverse reactions observed during the trial. This would have to be put down in agreements between the sponsors which would have to be verified by national competent authorities or Ethics Committees.

Preliminary appraisal: In view of the above, option 1 may be preferable, provided that:

- it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and
- it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised (see point 2.2).

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

MPA Answer: Yes

MPA Comment: **The goal to simplify procedures for Clinical Trials on Medicinal Products in EU not only necessitates more efficient and easily defined roles for National Competent Authorities/Ethical Committees, but also requires that the sponsor for a trial can be unambiguously identified. Preferably, a single Clinical Trial Application Form should be submitted for multinational clinical trials.**

2.6. Emergency clinical trials

This issue has been extensively explored in the 2009/10 public consultation (section 6) and discussed by stakeholders in their responses.
In order to address the situation, the Clinical Trials Directive should take into account internationally agreed texts (Declaration of Helsinki of the World Medical Association, the Convention on Human rights and Biomedicine of the Council of Europe, and the Guidelines on Good Clinical Practice of the International Conference on Harmonisation, 'ICH'). All these texts explicitly address the issue of emergency clinical trials.
In view of these texts, the Clinical Trials Directive could be amended to the effect that the informed consent and the information from the investigator may take place during or after the clinical trial under the following conditions: ¨

- The trial subject is not in a state to give informed consent;
- The physical or mental conditions that prevents giving informed consent is a necessary characteristic of the research population;
- Because of the urgency of the situation, it is impossible to obtain informed consent from the parents/legal representative (in case of adults) in accordance with the Clinical Trials Directive, and it is impossible to give the information, as provided in the Clinical Trials Directive;
- The trial subject has not previously expressed objections known to the investigator.

In this case, the informed consent would have to be obtained as soon as possible from the parents/legal representative (in case of adults) or the trial subject, whichever is sooner. The same holds for the supply of information to the trial subject.
All other rules for clinical trials (approval, safety reporting, etc.) would remain applicable.

Preliminary appraisal: This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.

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

MPA Answer: Yes

MPA Comment: **The existing directive makes no exemption for emergency situations when it comes to informed consent. In combination with national legislation this has caused a lot of problems in Sweden i.e. emergency clinical trials are in practise impossible to conduct. The MPA agrees that the proposal could be a way of addressing this problem. It is important that the new directive includes rules such as standards for acceptable study design and risk/benefit assessment for the protection of vulnerable populations. If references are made to internationally agreed texts such as the declaration of Helsinki, reference should be made to a specific version of the text.**

3. Ensuring Compliance with Good Clinical Practices in Clinical Trials Performed in Third Countries

This issue has been extensively addressed in the 2009/10 public consultation (section 7) and discussed by stakeholders in their responses.
As set out in the 2009/10 public consultation paper, any disregard of the rules that protect clinical trial participants is unacceptable and calls for determined action – independently of where the clinical trial has been performed. The Commission

is committed to ensuring that the fundamental ethical rules for clinical trials are applied everywhere. Any weakening of the standards with regard to third countries would be in contradiction to the fundamental principles of human rights and dignity and their universal guarantee and protection, to which the EU is fully committed.

Preliminary appraisal: In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of

- Clinical Trials, and
- Medicinal products.

Regarding the authorisation process for a clinical trial, this is currently addressed in point 2.7.2.4. of the detailed guidance CT-1[15] which provides that:

'*All studies* [submitted in the authorisation process of a clinical trial] *should have been conducted in accordance with the principles of Good Clinical Practice (GCP). To this end, the applicant should submit the following:*

- *a statement of the GCP compliance of the clinical trials referred to,*
- *where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. Where a clinical trial is not published in a register, this should be explained and justified.*'

Regarding the marketing authorisation process of medicines, this is addressed in point 8 of the introduction to the Annex of Directive 2001/83/EC, which provides that:

'*All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good* clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.'

The Agency is currently assessing various actions in relation to the implementation of this provision.

Both provisions, as well as implementation work could be further supported and supplemented through the following

Codifying, in the revised legislative framework the provision in point 2.7.2.4. of the detailed guidance CT-1 (see point above); and

Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database *EudraCT* and thus be published via the public EU-database *EudraPharm*.

In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database *EudraCT* and thus be published via the public EU-database *EudraPharm*

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

MPA Answer: Yes

No comments are provided by MPA

4. Figures and Data

The concepts discussed above are based on the figures collected by DG SANCO during the impact assessment exercise. These figures are annexed to this paper (not presented here in full). It is crucial that these figures are checked and complemented by stakeholders where possible and necessary.

Consultation item 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

MPA Answer: Yes

***MPA Comments*: The Annex summarizes data in the following tables:**

1. **Number of Clinical Trials in the EU**
2. **Number of multinational settings of clinical trials (EU)**
3. **Number of clinical trials per trial phase**
4. **Number of clinical trial participants (EU and global)**
5. **Number of planned clinical trial participants in the EU**
6. **Total number of clinical trial participants planned (for clinical trials with at least one clinical trial site in the EU)**

Tables 1 and 3 are to be used on the EU level and tables 2 and 4 are applicable both at EU and national level.

Tables 5 and 6 are suggested to be deleted as figures are uncertain.

Alternative or complementary presentation formats may be considered, e.g. histograms.

Additional comments on items mentioned in the Annex:

5. Staff figures in national competent authorities
Available resources may be described in FTEs but here only average values are given. Presentation of the distribution is warranted; i.e. mean, SD, median and range. The FTEs most probably differ between countries as the National Competent Authorities are organized differently according to local legislation and demands.

7. Estimated time needed for *sponsors* to comply with administrative requirements ('administrative costs')
This issue should be commented by the pharmaceutical industry. From a general view, the numbers probably depend on internal SOPs that vary between companies and further on the need for valid and complete applications providing time efficient assessments at agencies.

7. Insurance

Insurance is mandatory for the sponsor. In Sweden, there are we four types of insurances commonly used: “Läkemedelsförsäkringen”, covering claims according to injures from pharamaceutical drugs; “Patientförsäkringen”, covering injures obtained within the health care system; Insurance by “Kammarkollegium”, to be used by academic researchers and Insurances by “Zurich Insurances plc”, to be used by the pharmaceutical industry. In general these insurance are covering extra costs that may arise in relation to injures during care or within a clinical trial and level of compensation is in relative terms low.