

To: European Commission
DG SANCO/Pharmaceuticals
sanco-pharmaceuticals@ec.europa.eu

13th May 2011

Dear Sirs,

**Response of Janssen, Pharmaceutical Companies of Johnson & Johnson, to the
Revision of the 'Clinical Trials Directive' 2001/20/EC Concept Paper
SANCO/C/8/PB/SF/D(2-011) 143488**

Janssen, Pharmaceutical Companies of Johnson & Johnson (hereafter "Janssen") welcomes the Concept Paper submitted for public consultation on the Revision of the 'Clinical Trials Directive' and would like to thank the European Commission for the opportunity to comment.

Janssen has invested \$4.4 billion in 2010 on research & development and have a broad portfolio focussing on unmet medical needs across several therapeutic areas: oncology; infectious disease; immunology; neuroscience; cardiovascular and metabolism. As such, it has a huge interest in commenting on the Concept Paper provided by the European Commission.

In response to the questions presented in the Concept Paper, our comments are provided below:

1. Cooperation in assessing and following up applications for clinical trials

1.1 Single submission with separate assessment

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

- We believe a single submission would be more efficient and reduce the administrative burden of CTA applications, provided that additional national requirements would no longer be requested.
- If national documents, which comprise the main administrative burden of CTA applications, would need to be submitted through the EMA portal, this would complicate the process and result in prohibitively large submissions. In addition the timing of the submission of such national documents would need to be defined; as they are often only available significantly later than common documents required for all countries. A requirement to submit all documents simultaneously could therefore delay approval and subsequent commencement of the clinical trial.
- Harmonisation of electronic submission requirements would be an advantage of a single submission through a central portal, as compared to the increasingly divergent national requirements for electronic submissions existing currently.
- Functionality in the electronic submission to refer to previous submissions for the same product or protocol would be very helpful.

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

- We agree. Having separate assessments would undermine the advantage of a single submission because contradictory requests could still be issued by each Member State (MS). This would especially apply if there are different views regarding entry and exclusion criteria, primary endpoints, safety reporting.

1.2 Single submission with subsequent central assessment

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

- A single submission with central assessment would be feasible if the tasks of the National Competent Authorities (NCAs) and the Ethics Committees (ECs) are well defined. For example, the central appraisal could consider the scientific questions that are common for all countries, with national specific items being deferred to the ECs for assessment. However having a parallel national procedure for assessing ethical, national and local perspectives would again lead to divergence between MSs.
- Central assessment would reduce the resource burden on NCAs as only one entity needs to undertake the assessment instead of multiple NCAs. It should be possible to have a structure in place at the EMA to do the assessment without having to set up a formal committee similar to the CHMP.
- Central assessment could be considered appropriate for phase 3/4 trials (multinational studies involving more than 3 MSs). Also, a central assessment would be particularly relevant for paediatric studies being conducted after agreement of a Paediatric Investigation Plan (PIP).
- The option to choose a central assessment should be available to Sponsors of trials of all phases. If central assessment was mandatory however, separate (shorter) timelines would need to be defined, for example for Phase I trials and for single country versus multinational trials to maintain the feasibility of performing such trials in EU countries.
- A decreased fee structure could be established for academic researchers, which would be expected to overcome the concerns that the fees for a central assessment would be unattractive to these Sponsors. Academic researchers, in general, tend to run smaller, often single centre, studies.
- Although we recognise the potential advantages of a central assessment, we are concerned that it would be a lengthy procedure for both initial CTA applications as well as for substantial amendments. More information about the practicalities of a central assessment would help us to clarify its feasibility.

1.3 Single submission with a subsequent 'coordinated assessment procedure' (CAP)

1.3.1 Scope of the CAP

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

- Yes, the catalogue of areas/items to be considered in a clinical trial application is complete.
- We agree if items outlined in (b) and (c) are solely within the remit of the local Ethics committees only. However in some MSs these items currently fall within the Competent Authority remit, therefore if they were to remain within the CA remit, this could lead to a separate assessment by the local CA as well as the CAP. This would defeat the purpose of the CAP and lead to an increased burden rather than a reduction.
- In some MSs there are separate committees (e.g. first in human committee, viral safety committee) where authorisations/clearances may be needed before a trial can start. Clarification would be welcome regarding whether or not these assessments will be part of the CAP or an additional step.
- From the pharmacovigilance perspective a coordinated assessment of the labelling and investigator's brochure would further harmonise the reference safety information across the community for the purposes of safety reporting.
- Further information is needed about the procedure for handling safety signals, as well as substantial amendments or urgent safety amendments in the CAP.

1.3.2 Disagreement with the assessment report

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

- We believe that each of the proposed approaches has its pros and cons.
- The first approach would be probably the most workable solution. However, if a MS 'opts out' it raises the question of how a Sponsor would subsequently obtain a clinical trial approval in that particular country. It is also difficult to envisage a situation where a justification made on the basis of serious risk to public health or safety of the participant could be seen to apply in one MS but not in others.
- The second approach could prevent a clinical study proceeding in MS even if that MS is in preference for it to proceed. Likewise it seems unreasonable to force a MS to participate in a study if they voted "no".
- The third approach could lead to delays in study start up as it is often the case that one country requires modifications to a trial while other countries do not. If there is no decision making without referral in the process this will delay studies.
- For all options Sponsor should have the opportunity to withdraw an application at any point from a MS.
- Is there a procedure foreseen for the applicant to appeal a decision? If the first or second approach was used, would referral for EU level decision be needed in case of disagreement?
- For all options it raises the question of whether the Sponsor would be made aware of divergent opinions between MSs. We suggest that in line with increasing transparency any divergences are shared with the Sponsor.

1.3.3 Mandatory/optional use

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

- The CAP should be completely optional.
- The advantages of shorter review timelines offered by some countries would be lost if CAP is mandatory. For example for Phase 1 studies and smaller Phase 2 studies the CAP will likely delay the overall timelines. So if CAP was voluntary and national procedures are an option, Sponsors would continue to apply via the faster national route. In addition it raises the issue of whether current additional country specific committee still will be in place (first in human, viral safety etc) or if these would disappear.

1.3.4 Tacit approval and timelines

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

- In our view there is insufficient information to make a judgment on whether such a pre-assessment would be workable in practice. For instance, would there be an additional timeframe foreseen for this pre-assessment? Will it be a European or national assessment?
- Pre-assessment could prove challenging due to differences in local clinical practices and treatment guidelines at a local level. Variance/confusion in the interpretation of the above criteria could also occur.
- We are concerned about the predictability of such a pre-assessment. This additional layer of pre-assessment would provide an additional level of uncertainty regarding the approval timelines for these regulatory assessments.

2. Better adaption 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

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

- We agree that the definition of non-interventional trials should not be widened and that instead it would be better to devise harmonised and proportionate requirements that would apply to all clinical trials.
- Broadening the definition of non-interventional trials may lead to more non-interventional trials being regulated at the national level as they will fall outside of both the reporting requirements under the CTD and the reporting requirements under the new PV legislation, which may lead to further reduction in harmonisation from a pharmacovigilance perspective through differences between national reporting requirements for these types of trials. It is preferable to have a harmonised set of requirements where possible. Furthermore, one of the weaknesses identified in the previous 2009/2010 consultation related to current divergent views as to whether a trial is interventional or non-interventional. Although this may to some extent be rectified through a single or coordinated assessment procedure, the regulatory

framework may further benefit from additional clarity on the definition of each type of study.

- It may also be helpful to further clarify the definition of “non-interventional trials” as the divergence may be due to lack of clarity.
- Differences between national clinical practices may still result in different assessments of interventional versus non-interventional status.

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

- Yes we agree with this appraisal. The same requirements should be applied irrespective of nature of Sponsor to ensure patient welfare and safety.
- In order to decrease the burden for academic sponsors, it would be better to develop harmonised and proportionate requirements for clinical trials, independently of the nature of the sponsor so that they all fall under an improved, truly harmonised clinical trials directive.

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

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

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

- We agree with this appraisal. The current challenge is a lack of implementation of central rules at national level, still leaving divergence in requirements on a per country basis. It would be helpful if there were some way to assign timelines for national implementation.
- The detailed guidance on submission of clinical trial authorisation applications is a very useful document and annexes to the basic legal acts would be a good start to encourage harmonisation. However we are concerned that it will not be sufficiently binding to the national agencies as the national agencies will give their own interpretation. Only once guidance's are fully accepted by the different MSs without exceptions or differences, can greater harmonisation be achieved.
- Detailed provisions on safety reporting in the Annexes to the basic legal act would be welcomed. This would further reduce inconsistencies and consequent administrative burden in ADR reporting under the CTD across the Community due to divergent interpretation and implementation of the current rules.
Specifically, we would welcome provision for direct reporting to the EVCTM, this would bring requirements for reporting in closer alignment with recently revised 2001/83/EC and greatly reduce administrative burden by creating a single harmonised reporting process for multinational studies. As expressed in previous comments to the 2009/2010 consultation and CT-3 revision consultation, currently ADR reporting in the various MSs is not harmonised, and there is a serious disconnect between the requirements of the clinical trials directive and post-marketing reporting requirements. Reducing requirements for individual SUSAR reporting to regulatory authorities only, and retaining annual reporting and reporting of serious issues to ECs (and investigator as appropriate) across the community could significantly reduce the administrative burden while properly ensuring monitoring of patient safety. This could be done by making use of the DSUR for reporting to ECs and investigators.

Additionally, further clarification on the Commission's framework for risk-adaptation is requested (e.g. what specific criteria are considered; how is "risk to trial subject safety" and "risk to data reliability and robustness" to be defined; how will the risk adapted rules be applied in practice; and is this to be linked to GCP?) If not clearly defined, application of the rules could become quite complex, thereby increasing administrative burden for both industry and regulators.

Other key aspects on which detailed rules are needed:

- Breaches to GCP
- Importation rules for Investigational Medicinal Products
- Exportation rules for biological samples
- Classification of amendments as substantial or non-substantial.

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

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

- We largely agree with the proposal outlined in the Concept Paper, in particular a narrowed definition of investigational medicinal product is welcomed. We also agree about the uncertainties of classification of non-investigational medicinal products (nIMPs) and the need for establishing clarity for their proportionate requirements. However the creation of the term "auxiliary medicinal product" raises the question - does the term auxiliary medicinal product replace the term nIMP or is it a term that is intended to be used as well as nIMP? We would advise against introducing a third category of products used in clinical trials as this would increase the complexity and the opportunity for confusion. It is essential therefore that there is a high degree of clarity regarding what products fall within the definition of "Auxiliary Medicinal Product".
- We strongly believe that add-on therapies and background therapies given to all patients as well as ancillary materials such as infusion/saline solutions etc. should explicitly be categorised as 'auxiliary medicinal products'. PET tracers used as a diagnostic agents and other diagnostics should also be included in the list of auxiliary medicinal products.
- The acceptability of this proposal is dependent on the proportionate requirements for "Auxiliary Medicinal Products" being reasonable, practical and proportionate to the risk related to their use in the trial. Also critical for this proposal's acceptability is a consistent application of the requirements across all MSs.

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

- In our view neither of the policy options suggested is appropriate to address this issue.
- Removing insurance/indemnisation requirements for low-risk trials will lead to divergences in interpretation as it is difficult to find objective criteria for determining that an interventional trial is of low risk. Even low-risk trials still have some risk and need insurance. It is anticipated that many companies would not conduct a "type-A trial" if insurance was removed since due to the increased risk.

- It is not clear how an optional indemnisation would work in practice and who would be responsible for coverage. Clarity and/or harmonisation should be encouraged regarding differing national insurance expectations (scope; level of cover).
- Investigator insurance should also be considered.

2.5 Single sponsor

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

- We agree that maintaining the concept of a single sponsor is the clearest approach and the most straightforward.
- With particular emphasis on point 3 in the concept paper under “assessing the possibility of ‘multiple sponsorship’...” – it must be clear that one party needs to be responsible for notification of SUSARs in this type of situation. Otherwise, there is a serious risk of duplicate reporting leading to an increase in unnecessary administrative burden, which would inevitably impact the quality of the accumulating safety data. (There may be situations where responsibilities are shared; one party reports in some regions/countries and another in others – this is acceptable as long as clearly defined).

2.6 Emergency clinical trials

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

- We agree with this appraisal. Clarity over re-consent should be included.

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.

- We agree with proposals 1 & 2 although with some additional clarifications. We have some reservations concerning the third proposal.
- Further clarity is needed around proposal 2. Specifically whether there is an expectation that the Sponsor will be responsible to support ‘capacity building’ and the form that this may take.
- Whilst it is preferred to have European representation in clinical studies, this is not always possible. As long as there is evidence that the studies have been conducted appropriately and that the data is extrapolatable to the EU population, this should suffice.
- It seems to be an additional administrative burden to have all clinical trials registered in EudraCT as well as to include additional documents into the submission.
- Studies should not be excluded on the basis that their details are not in EudraCT as this could potentially impact the treatments/indications being registered in Europe. Other clinical trial databases exist (e.g. clintrials.gov) and duplication of the content of such databases should be avoided.
- It is difficult to see how the third proposal could work – registering the trial in EudraCT would require an overhaul of system and raises the question of what the

reporting requirements would be if there were no sites in the EU (e.g. Tropical diseases).

4. Figures and dates

Consultation item no. 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.

- Although the implementation of the Clinical Trials Directive provides a common platform on the performance of clinical trials, we cannot say that the approval timelines have been improved compared to the situation prior to the clinical trials Directive. The various local requirements (e.g. approvals from Hospital Scientific Committees as a prerequisite for National EC submission, the signing of the Contract etc.), make the process of trial approval/set-up time consuming- it may take 5-6 months from the moment the final protocol is available. Therefore practically, with regards to timelines, the benefit from the implementation of the Clinical Trials Directive is lost.
- We don't have any "hard" data currently available. The time and resources required for the initiation of multinational clinical trials vary from country to country and depends for example on the CTA review/approval process. Considerable time is spent during the CTA preparation phase on the follow up and collection of the local documentation to include in the CTA or in the application of the amendments.

Yours faithfully,

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