REVISION OF THE 'CLINICAL TRIALS DIRECTIVE 2001/20/EC

BRISTOL MYERS SQUIBB RESPONSES AND COMMENTS IN RELATION TO CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

(Reference SANCO/C/8/PB/SF D (2011) 143488)

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS.

Single submission with separate assessment

"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.

Response: YES. In addition to reduce the administrative work, this would also drive consistency across EEA countries by eliminating the country specific required documents for the CA submissions. As a general note, whatever proposal is put forward, it will only work if countries DO STOP requiring additional pieces to the Clinical Trial Application CTA dossier in addition to the ones required by the EU CT Directive and associated guidance.

Single submission with separate assessment

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

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

Response: YES. Indeed the single submission while reducing the administrative burden will not solve administrative and/or duplicated efforts in addressing multiple assessments and CA Inquiries.

Single submission with subsequent central assessment

"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. 1 200) 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.

<u>Response</u>: YES. While the central assessment does make sense for the Centrally Authorized Procedure and that the concept is very attractive, it is not appropriate for Clinical Trials: this will cause undue delays as each of the 30 countries impacted could potentially comment and inquire the CTA dossier knowing that the average number of participating countries is 5.5 per trial.

In the current concept paper to revise the EU Directive, the creation of a Community CTA review of trials to be conducted within the EEA as a complement to the present regulatory framework is not relevant. Consensus is indeed that only participating countries in a given trial must be consulted for the review and approval of the CTA and similarly countries not targeted for a given Clinical Trial should not be offered to review the CTA. The proposed CAP could be further fine-tuned, i.e. 1- clarify what is meant by "lead to a 'single decision' per Member State which would include the

aspects assessed in the CAP". We think that the CAP should not have a National Approval Step by CA2- offer the possibility to have an expedite approval for any MS being added into the Clinical Trial after the completion of the CAP.

Single submission with a subsequent 'coordinated assessment procedure'

"… 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 labeling…
b) Ethical aspects related to informed consent, recruitment and reward…
c) Local aspects related to suitability of sites, the investigator and national rules…"

Only the aspects under point a) would be suitable for the CAP. In particular, the aspects under b) and c) are not suitable for the CAP as the 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?

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

Consultation item no. 4:

Response: YES. The CAP is built on the experience gained from the Voluntary Harmonization Procedure VHP proposed to the Sponsors in 2008. BMS did submit one study in this model. The outcome was very positive and we could experience the advantages of the submission of one core dossier together with a coordinated assessment leading to only one set of CA Inquiries. The established timelines were adhered to and overall the approval of the study did not take longer than as per the usual process.

The catalog is complete and we do understand that the CAP would only concern the CA submission, i.e. excluding the EC submission and review. Therefore a clear line on respective EC & CA responsibilities has to be drawn. In summary, the National Rules should only cover the ability for a given site to conduct a study. If we go beyond this we would lose the benefit to go through the CAP.

Consultation item no. 5:

Response: YES. We do agree with this, foreseen that all other aspects as detailed in point 1.3.1 b) & c) (Scope of the CAP) are clearly referred as being within the scope of the Ethics Committees and therefore explicitly excluded from the CAP scope. To supplement this statement, it is important to note that aspects such Data Protection or Patient Informed Consent (ICF) are still Nationally Regulated and legally driven.

In order to emphasize the need to have a harmonized patient protection within the EEA, initiatives should be made/pursued to have more consensus on the Data Protection rules and content of the ICF.

Resolving disagreement amongst Member States

The concept paper proposes three approaches for resolving disagreement amongst Member States about the assessment as follows:

(1) 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'; or

(2) the Member States concerned could vote on the issue and decide by simple majority; or

(3) 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.

Response: None of the 3 approaches. Approach (1): whenever one MS rejects a study on the basis of a 'serious risk to public health or safety of the participant', this should apply for all MS, i.e. one cannot consider having the same trial being rejected in one MS while authorized for conduct in the other MS on the basis above.

We should consider the current community practices for Decentralized Procedure DP/Mutual Recognition Procedure MRP as to define the best approach here. This should be a hybrid between approaches (2) and (3):

- **MS first have to debate and reach a consensus**
- **In case of disagreement, they should vote**
- **If the majority is not reached, the matter should be referred to the Commission or the Agency**

The latter will or will not authorize the Clinical Trial to be conducted in the proposed list of countries.

Mandatory or optional use of the Coordinated Assessment procedure

The CAP could be mandatory for **all** clinical trials **or all multinational** trials **or completely optional.**

Consultation item no.7: which of these approaches is preferable

Response: Preferred approach is (2). We should avoid establishing too many systems/models in parallel. We should limit the options and rules for the Sponsor and participating MS, i.e.

- **a single country clinical trial is authorized by the National CA on the provisions of the CT Directive**
- **a multinational clinical trial is authorized through the CAP.**
- **Note: if a country is added after the initial approval by a NCA, this Clinical Trial should enter the CAP. The initial approval as granted by the NCA will be part of the CTA package.**

Again this applies the rules of community practices, e.g. MRP.

Tacit approval and timelines

It is proposed that the CAP be based on the concept of an obligatory single authorisation per Member State prior to the commencement of the clinical trials, that the timelines should not be longer than 60 days 'as a general rule', and that the timelines could be shortened for so called 'type-A trials' which could be identified as such "in a pre-assessment" on the basis of several criteria.

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

Response: The distinction between "type-A trials" and other trials makes a lot of sense. The pre-assessment step should be done by the Sponsor prior to the submission. Once done the CTA should be automatically routed to the faster review process. The Sponsor should carefully make this assessment and if Type-A trial is confirmed, a justification should be provided in the CTA dossier.

The pre-assessment step should not trigger any delays as to jeopardize the benefit of having this shortened review period.

We are also questioning the following part of the definition of the Type-A trials - "used within the authorised indication; or part of a standard treatment in a Member State

concerned": Are we still speaking about IMP here given the above definition? This could be extended to IMP authorized in a MS but used out of label. While referring to the definition of the Investigational Medicinal Product (IMP), it states that an IMP is a product (...) assembled (formulated or packaged) in a way different from the authorised form, or when used to gain further information about the authorised form. It should be acceptable to include those IMPs in the Type A trials foreseen(a) The safety profile of all investigational medicinal products used in the trial is sufficiently known and (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.'

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

Limiting the scope of the Clinical Trials Directive

Enlarging the definition of 'non-interventional trials'

"*Rather than limiting the scope of the Clinical Trials Directive through a wide definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which could apply to all clinical trials falling within the scope of the present Clinical Trials Directive."*

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

<u>Response</u> : YES. The scope of the current Directive is adequate. The main goal of the present exercise is to achieve the harmonization across Member States which remains the basis for the appropriate functioning of the EU CT Directive. Changing the scope by adding some more definition will again open rooms for interpretation.

Limiting the scope of the Clinical Trials Directive

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

"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. The proportionate requirements would apply independently of the nature of the sponsor ('commercial' or academic/non-commercial')."

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

Response: YES. One of the most recognized benefits from the EU CT Directive is to have brought Commercial and 'non-commercial' trials to the consistent level in term of Patient Protection and Transparency in the requirements for the start-up and study conduct. The Type-A trials is a more appropriate distinction to be made indeed independently of the nature of the sponsor.

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

"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.

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

Consultation item no. 11:

Response: YES. The proposed use of the Annexes to the basic legal acts is questioned. While their use will better guarantee the consistent rules across Member States, the revision of Annexes is a lengthy process. The use of Guidance to serve the purpose of

setting out provisions on a risk-based approach and greater harmonization will offer more flexibility whenever revision is needed

Consultation item no. 12

Response:

- **Do we refer to the Type-A trials proposed in section 1.3.4? The same concept and terminology should be used while addressing requirements both for the Study Start Up and the Study Conduct, e.g. Safety Reporting, Substantial amendments..**
- **The requirements in term of Safety Reporting significantly differ from one MS to another. Detailed and consistent rules across the Member States should be defined for:**
    - **Reporting of SUSARs e.g. some EEA CAs want only domestic cases, others all SUSARs**
    - **SUSAR reporting to CAs for IMP with Marketing Authorization MA**
    - **SUSAR reporting for IMP with the MA Holder being the Sponsor, e.g. the need or not to report serous related cases to the MA, as required by UK MHRA**
    - **Reporting of SUSARs to ethics committees (overlap with what reported to CAs)**
    - **The timing for semiannual SUSAR reports to CAs and ECs. Not sure there is much concern here, except that the SASUSAR report goes to both HA and ECs i.e. duplication**
    - **Harmonized format for the ASR**

Clarification about the Safety reporting requirements for NIMP. Note, EC guidelines on IMPs and NIMPs have recently been updated , but these refer to Volume 10 for reporting adverse reactions, which does not provide much advise for NIMPs.

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

A cumulative approach is proposed to address the issues resulting from legal uncertainties surrounding various aspects in relation to above matters

"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.

<u>Response</u>: YES. We are strongly in favor of narrowing the IMP definition. But this will not remove ambiguity about the NIMP - now named Auxiliary Medicinal Products. The key point is the consistent approach across Member States. See also BMS answers to Item 11 (Use of Guidance versus Annex) and Item 12 (Safety reporting).

Insurance/indemnisation

Two policy options are proposed for addressing the identified issue:

- "Removing insurance/indemnisation requirements for low risk trials"
- "Optional indemnisation by Member State"

"Both policy options could be a viable solution"

Consultation item 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

<u>Response</u>: The concept to start differentiating is questioned here. We do not believe that this will have an impact for commercial sponsors as the insurance policies we subscribe are for all clinical trials we conduct. It is only in some countries that we need to notify trial by trial. This is a requirement as per ICH 3. 2.F . The insurance coverage has to be adequate and related to the risk of the trial. In other words, some risk assessment is done by the insurance provider. In addition Option 1 will face objections from Ethics Committees.

Single sponsor

Two options are proposed as follows:

- "Option 1: maintaining the concept of a single sponsor
- Option 2: allowing for ac 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 trail in a Member State"

"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"*

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

<u>Response</u>: YES. For clarity reasons we would recommend to maintain a "single sponsorship". In case of joint development the roles of co-sponsors and their responsibilities should be shared through other contractual agreements clarifying the contractual arrangement. Designating one Sponsor decreases the level of complexity and favours a streamlined approach in terms of CTA filing and contact with EC and/or the national competent authorities. Additional clarification should be provided as to what - at a minimum - has to be secured by a Sponsor in case of Joint development, e.g. in the instances where a development program is managed by a company and Sponsored by another Company.

Emergency clinical trials

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 (conditions listed in the Concept Paper submitted for public consultation)

"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.

Response: YES. We do agree with the appraisal. Key to the issue remains that a legal representative is in most countries not defined for healthy persons. A legal representative can only be determined by court. BMS agrees that having the consent during or afterwards is a realistic solution. The IEC will have an important role to assess whether such a process in the targeted population is appropriate.

ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

"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……"

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

Response: YES. However the point 3 is not clear. Today the only trials exclusively conducted in third countries (i.e. ex-European Economic Area EEA) registered in EudraCT are the Paediatrics trials part of a Paediatric Investigation Plan (PIP). Is it the intent to extend this to all trials? In theory this is feasible but will increment a significant additional workload and procedural change at the Sponsor level. Also definition of Third Countries should be given.

Consultation item no. 18: Figures and Data.

We do not have additional data to the ones provided to the Consultation paper 2009/10.