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European Commission
Health and Consumers Directorate-General
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REVISION OF THE CLINICAL TRIALS DIRECTIVE 2001/20/EC CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION: CELGENE International contribution

Celgene is a multinational biopharmaceutical company engaged primarily in the discovery, development and commercialization of products for the treatment of cancers and other serious diseases. Headquartered in New Jersey, USA, Celgene operates in 18 European Union (EU) Member States and currently has over 30 clinical trial programs running in the EU. Celgene is working in partnership with many European academic centers. As a company committed to clinical development of innovative medicines, we believe that the revision of the Clinical Trials Directive is necessary and an opportunity to improve the state of European Clinical Research, ultimately to the benefit of patients. Accordingly, Celgene appreciates the opportunity it has been given to comment on this concept paper.

Consultation Item no. 1: single submission of the clinical trial application
Celgene's answer: we strongly support the principle of a single submission. It is a key aspect of the reduction of the administrative burden to be able to perform all necessary Clinical Trials Applications (CTA) in a single submission based on a unique set of documents valid throughout the entire EU. The revised legislation should ensure the content of the CTA is binding to all Member States (MS).

It is indeed of a paramount importance to avoid in the revised legislation that MS impose specific additional documentation requirements as has resulted from the transposition of the current Clinical Trials Directive (CTD) into national law. Those divergences in requirements and processes, which appeared across countries and continue changing across time, have considerably complicated the registration of clinical trials in the EU. This is especially relevant for the multi-country trials, which have gathered around 70% of the enrolled subjects in 2010 across the Union and represent the quasi totality of Celgene's clinical trials.

Consultation Item no. 2: separate assessment of the application
Celgene's answer: we agree that a separate assessment will not be sufficient.
Although of a more limited importance when compared to the issue mentioned under item number 1, the fact that the same application is being reviewed multiple times creates the risk that divergent requests to amend the protocol are being made across EU Member States. When such an issue occurs in a multi-country trial, the need to maintain a single protocol across all the concerned Member States may force the sponsor to withdraw the application in a given country. Such a decision gives rise to differences in the access to innovative treatments across the EU.

Consultation Item no. 3: single submission with subsequent central assessment
Celgene's answer: In essence, a central assessment of submitted CTA dossiers is the most logical approach from a methodological standpoint. The concept has proven its effectiveness with marketing authorizations. On the other hand, given the relatively low proportion of clinical trials being run in a truly large number of EU Member States, one could wonder whether a centralized assessment systematically involving all the Member States, regardless of the countries where the clinical trials are to be conducted, may not end up on an heavy, long and finally counterproductive process. This may, in particular, occur if, the central authorization would have to be granted by the Commission through the commitology process.

In addition, it may be difficult for the Member States to convince their public opinions that a non national authority is equally or better qualified than the national authorities to approve clinical trials to be conducted in their territories. That difficulty may be a serious obstacle to the acceptance of the new procedure by the Member States.

Given those circumstances, a central assessment may not be the most pragmatic approach in order to achieve a **rapid** correction of the declining European clinical research. Therefore, we may concur with the assessment set out in the concept paper.

However, the concept of a central assessment should not be discarded in the long run. This is why we recommend that the Commission includes in its legislative proposal the principle of a reevaluation and, if necessary a revision of the procedure, e.g. along the lines: "*The Commission shall report, for instance within 5 years after entry into force of the revised legislation, on the functioning of the CAP and review whether a central assessment process would be advisable.*"

Consultation Item no. 4: Scope of the CAP. Do we agree with its definition?
Celgene's answer: The concept of the CAP seems indeed to allow for an interesting level of flexibility. It may offer a solution more acceptable to the Member States than the central approval and, accordingly, allow a quicker revision of the legislation.

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We agree with the proposed scope provided that the completeness and adequateness of the CTA dossier is clearly included under point (a) of Section 1.3.1 of the concept paper, *i.e.* the aspects which would be suitable for the CAP. It is essential that the documentation requirements for a CAP are strictly identical across the whole Union in order to avoid "Member State shopping," i.e. a situation where the applicants submit most of their applications to Member States with the less burdensome requirements. One can expect that this situation will chronically clog the system.

We would therefore propose to add the following under point (a):
"- *completeness and adequateness of the Clinical Trial Application dossier*"

We also propose to replace the points

- the design of the trial;
- the relevance of the trial, including the credibility of the results;

as follows:

"- *the review of the protocol (including, the design of the trial ; the relevance of the trial; the credibility of the results, IMP/non IMP categorization of medicinal products used in the conduct of the trial etc…)*"

Consultation Item no. 5: Agree with scope exclusions?
Celgene's answer: we agree to exclude points b) (ethical aspects) and c) (local aspects) from the scope of the CAP in order to allow national Ethics Committees (ECs) raising and addressing specific ethical concerns about the conduct of clinical trials in their countries. However, the allocation of responsibilities between the ECs and national competent authorities (NCAs) should be clearly defined in the legislative proposal. Otherwise, it will be impossible to avoid divergent interpretations about the assignment of responsibilities and, unavoidably, different documentation requirements will emerge. Another concern is how those MS where ECs act as the NCA should work within the CAP. How their role within the CAP and their Ethical role would be coordinated / distinguished from each other?

Consultation Item no. 6: resolution mechanism in case of disagreement. Choose and justify.

Celgene's answer: We would prefer Option 1 (Member States could be allowed to 'opt-out') because we see it as a way to gain acceptance for the proposal at the Member State level.

However, the "opt-out" option should be reserved for exceptional cases. We agree that the Commission's legislative proposal should provide that the Member State(s) can only opt-out because of a serious risk for public health or the safety of participants. The legislative proposal should clearly define what a "serious risk for public health or the safety of participants" is or provide for adequate criteria. We believe that the European Commission's Guideline on the definition of a potential serious risk to public health in the

context of Article 29(1) and (2) of Directive 2001/83/EC could be a useful model for establishing such a definition (see OJ C 133, 8.6.2006 p. 5).

We believe that this approach provides a "safety valve" to the CAP while at the same time limiting the opportunity for a NCA to use its opt-out rights inappropriately. Without those limitations to the Member States' opt-out rights, minor or moderate Member State disagreements with a Coordinated Assessment could give rise to a proliferation of country specific protocols.

Consultation Item no. 7: mandatory or optional use of the CAP
Celgene's answer: we prefer the second option, i.e. "CAP mandatory for multinational clinical trials" in order to generalize the use of a system based on a single set of required documentation.

In order to ensure a smooth transition, we suggest a test period of, for example, three years during which the CAP would be optional. After that period, the CAP would become mandatory for all multinational trials.

We suggest that the revised legislation includes a clear definition of "multinational trial," for example "*a clinical trial conducted in 3 or more Member States*."

At any rate, a single set of documents should be required for the national procedures and the CAP. Otherwise, the Member States will continue imposing burdensome country specific documentation requirements upon the applicants. In addition, during the transition period, it should be clear that the CAP should be the choice of the applicant and not at the discretion of the NCAs.

Consultation Item no. 8: Risk based approach for Type A trials. Agree with concept? Agree with measures (shortened timeline)?
Celgene's answer: in essence, we agree with the proposal. There are indeed a large number of trials, especially those conducted by academia, which trigger a low level of risks for the patients in addition to the risks of standard medical practice. Those trials are important to refine medical practice. It seems, thus, logical to facilitate the conduct of those trials by applying shorter timelines. Criteria should be clearly defined in order to determine the 'low-risk' profile of a trial. For instance, a 'checklist' for the pre-assessment procedure would be useful in this context.

Consultation Item no. 9: Non-extension of the definition of non-interventional trials
Celgene's answer: we agree with the preliminary appraisal: an extension of the concept of 'non-intervention trials' would weaken the impact of the revised Clinical Trials Directive in terms of legislative harmonization.

Consultation Item no. 10: Non-exclusion of academic or non-commercial trials from the scope of the Directive
Celgene's answer: we strongly agree that it is important to keep academic or non-commercial trials within the scope of the revised Directive in order not to introduce inappropriate differences between patients with respect to medical care standards.

Non-commercial trials are essential for opening new paths in the development of medical practice. The exclusion of non commercial trials from the scope of the Clinical Trials Directive would drive the pharmaceutical industry to re-do those trials for registration purposes, which would give rise to obvious ethical concerns.

Consultation Item no. 11: Proposal to harmonize and simplify the content requirements for clinical trial applications and safety reporting. Proposal to delegate power to the Commission to establish or update such requirements.
Celgene's answer: We strongly support this suggestion.

We believe it is very important that a legislative proposal to revise the Clinical Trials Directive provides risk-adapted rules on the content of the clinical trials application dossier and on safety reporting which would be the same in all EU Member States.

It makes sense to include those rules in Annexes to the basic legal act and to delegate to the Commission the power to establish or amend these requirements through delegated acts. If the delegated acts take the form of Directives, they should not, in our view, allow that Member States introduce additional requirements.

Delegated acts could also have the form of Regulations[1]. Because Regulations are directly applicable, those delegated acts would ensure a more consistent application of the CTA dossier and safety reporting requirements throughout the EU.

We also strongly support the rationalization of the safety reporting (for products under development for the treatment of life threatening disease) to focus on events of concern at an agreed level of severity.

Consultation Item no. 12: any other key aspects?
Celgene's answer: No comments

[1] Examples of Commission Delegated Regulations supplementing a Directive in other areas include Regulations 1060/2010, 1061/2010 and 1062/2010 regarding energy labeling of domestic appliances.

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Consultation Item no. 13: IMP vs. AMP (auxiliary MP)
Celgene's answer: it is our position that this appraisal is an improvement as compared to the current situation. However we believe that the revision of the legislation should be an opportunity to go further in the simplification. In that respect, we do not believe it would be useful to introduce a category of AMPs subject to a derogatory regulatory regime.

We believe that it would be more effective to define more accurately which medicines should not be considered an IMP. A lot of confusion has arisen from the current definition of IMPs. On the basis of that definition, many national authorities consider any reference standard therapy provided in the context of a clinical trial as an IMP. Those standard therapies have been established in many cases as standard of care for over decades and are not subject to any further investigation. Considering those standard therapies as IMPs obliges the sponsor to report adverse reactions related to well established treatments to the authorities, ethics committees and investigators. Those reports will burden the recipients with a huge amount of information which is not relevant to the benefit-risk assessment of the clinical trials.

We understand that it may be appropriate to consider comparators or concomitant medicines as IMPs in some - infrequent –circumstances. That may, for example, occur when the pharmacokinetic interactions between the IMP and a concomitant product are studied. The legislation should indeed take into account those exceptional situations. However, comparators and concomitant medicines which are used in line with the standard of care should, in principle, be considered **non** IMPs.
In that respect, shall be considered standard of care, treatments generally provided by the specialists concerned, including care provided in accordance with guidelines of public health authorities or medical societies, authoritative medical text books or journals.

The classification of a product as IMP/non IMP should be included in the scope of the CAP, in order to avoid the risk of divergent local interpretations as seen currently (see proposal under consultation item 4).

Consultation Item no. 14: Risk based proposal to lower insurance requirements. Chose and justify.
Celgene's answer: No comments.

Consultation Item no. 15: Co-sponsorship. Proposal to stay as-is.
Celgene's answer: we do not agree with the proposal to remain with single sponsorship as the only option. In order to facilitate some multicountry cooperative trials, we believe it is important to allow for some level of controlled co-sponsorship and a number of solutions which clearly define the responsibility of each sponsor could be put in place.

For example, a provision similar to the following may address the concerns raised by some stakeholders with respect to co-sponsorship:

"*Without prejudice to the civil and criminal liability under the law of the Member States, the responsibilities of the sponsor under this Directive may be assumed by more than one sponsor provided that the assignment of the sponsor responsibilities between the co-sponsors has been set out in clear, detailed and written arrangements which bind the co-sponsors contractually. In particular, the co-sponsors shall specify in those arrangements who, of the co-sponsors, shall have the ultimate responsibility for the provision of authoritative information about the clinical trial (for example with respect to adverse reactions arising from or the status of the trial) to the competent authorities of the Member States.*"

Co-sponsorship agreements should be included in the CTA application and their assessment should be part of the CAP.

Consultation Item no. 16: emergency clinical trials
Celgene's answer: No comments.

Consultation Item no. 17: GCP in third-countries
Celgene's answer: No comments.

Consultation Item no. 18: figures and data
Celgene's answer: No comments.

Yours sincerely,
Celgene International.

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