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European Commission
Enterprise and Industry Directorate-General
Via e-mail to entr-pharmaceuticals@ec.europa.eu

ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC – Public consultation paper

CELGENE Corporation Contribution

Celgene Corporation, headquartered in New Jersey, USA and operating as well in 19 EU Member States, is an integrated global biopharmaceutical company engaged primarily in the discovery, development and commercialization of novel therapies for the treatment of rare cancers and inflammatory diseases. Celgene currently has 24 clinical trial programmes running in the EU and works in partnership with many European academic centers, something particularly important in the field of rare diseases. It is from this perspective that Celgene Corporation, hereby represented by Celgene International, its Swiss based affiliate operating the international activities of the Celgene group, including in the European Union, would like to thank the European Commission for this opportunity to comment on the future of Clinical Trials in Europe.

In the following contribution, responses are given only to the points where the Company felt it needed to add to the assessment of the consultation paper or should provide an answer i.e.: not all Issues/Consultation Items are addressed in the below response.

Key issue #1: multiple and divergent assessments of clinical trials
Consultation item #4: quantify implications of each option. Which practical legal aspects to consider?

The consultation paper proposes several options, from the existing Voluntary Harmonization Procedure (VHP) to a range of streamlined procedures, inspired from the marketing applications ones.

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The VHP is a commendable initiative for short term improvement of the current situation. However, in the long term, if the EU is to remain competitive, the trial sponsor must, through the provision of a single application, be able to seek an authorization to conduct a clinical trial valid in the whole European Union.
Therefore, our preference would be to have two possible routes based on the same documents requirements:

- one de-centralized procedure, ultimately replacing the VHP,
- and one centralized procedure.

These two European wide applications would be managed by one single evaluation process.
The centralized/de-centralized process for clinical trials applications could be modeled on the existing procedures for centralized marketing applications, and therefore managed by the European Medicines Agency.

The advantages that we see in such an approach are numerous. In particular:

- **Expertise.** Possibility to ensure the highest possible standard of the assessment by drawing on the specific expertise available across the Community which may not necessarily be available in each Member State. This improvement will directly benefit clinical trial participants. The same specialized team could work in partnership with the sponsor, from the scientific advice until after the conduct of the Clinical Trial i.e.: the marketing application, thereby providing additional benefits.
- **Maximize resources and consistency**. One central procedure would prevent resources spending by each concerned member state for the same assessment and would allow a single consistent approach. Indeed, inconsistencies and lack of resources have historically led to delays and also put heavy burden on both the competent authorities and trial sponsors – especially academic centres and SMEs. A centralized procedure should result in quicker access to trials for patients across the EU as an approved CTA would be immediately valid throughout the whole community area. It may ultimately lead to faster access to approved medicines and will support innovation and competitiveness in the EU to the highest degree possible.
- **Ethics Committees (EC) and assessment team communication.** EC issues with protocols would be discussed with the assessment team if they could not be resolved with the sponsor. The benefit of one reference point in this respect would increase consistency across countries and also reduce delays.

The practical aspects that would have to be considered include:

- Ability for the sponsor to choose the most appropriate route, e.g.: in case of one or two members states involved, proceed via the de-centralized procedure and if

high expertise and/or multiple member states involved, follow the centralized process.

- Sufficient resource allocation or commitment from National Competent Authorities (NCAs) to ensure fixed timelines are met. To that regards it should be noted that significant reviewing resource will be freed up via the avoidance of repeated evaluations of the same CTA in all NCAs,
- Ethics Committees approval will still have to be gathered separately. However, the EU community and especially patients would also benefit from a common operating structure of ECs, e.g. one national EC instead of regional or hospital specific ECs. In addition, a process whereby ECs could discuss with the assessment team if an issue could not be resolved with a sponsor would assist in providing some greater consistency in EC opinions.
- In case of disagreement between the sponsor/applicant and the assessing agency, an "arbitration like" procedure would need to be setup for resolution for both the de-centralized and centralized procedures.

Key issue #1: multiple and divergent assessments of clinical trials
Consultation item #5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

The consultation paper lists three options aimed at improving the ethical review of a CTA:

- single submission that can be used for NCA and Ethics Committee (EC)
- Strengthening networks of national Ethics Committees involved in multinational clinical trials
- Respective NCA and EC assessment scope clarification

It is our opinion that these options are not mutually exclusive and could be implemented in parallel. It appears indeed that, as opposed to scientific assessment of a CTA, the concept of ethical assessment is more difficult to spread from regional or even national considerations. It is therefore likely that a national EC approval will remain a requirement independently of the evolution of the legislation. To that regards, any initiative aiming at streamlining the procedures related to EC would be desirable.
Another proposal would be revised legislation to set minimum standards and guiding principles for EC members selection and training. It may also be desirable to establish high level ethics principles applicable to clinical research throughout the whole Community.

Key issue #2: inconsistent implementation of the Clinical Trials Directive
Consultation item #8 Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

In our view the Clinical Trial Directive should be replaced by a new Regulation Indeed we see local variations in implementation of the current Directive as the root cause of the issues now faced. We believe the objective of creating an EU wide CTA authorization can only be successfully achieved via a single text that would be binding to all European ECs and NCAs.
In addition, although the current text of the directive indeed requires clarification and updated implementing guidelines, these should be integrated into the future regulation. Should these be brought into a revised version of the directive: for instance, a clearer definition of the characteristics of a substantial amendment, there is no guarantee that they would not be altered when transposed nationally. It seems logical to think that the same pattern of inconsistencies resulting from national variations in transposition would perpetuate until a unique, agreed upon text can be promulgated.

Key issue #3: regulatory framework not always adapted to the practical requirements.
Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

It is our opinion that the EU Clinical Trials Directive was a very good step forward and that its introduction was a major milestone in the EU. However, a revision of the current guidelines in isolation would not address the problem in a satisfactory way and resources and time would be taken up for a short term solution not able to fundamentally address the long term root causes.

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

Our position is that by excluding "academic" sponsors from the scope of the Clinical Trials Directive, this would be contrary to one of the Directive's primary objectives; to ensure that all clinical trial subjects are afforded the same high standards of welfare and safety.

There is also a high risk that such distinction may lead to double standards in clinical research in terms of study quality and data credibility. There is a risk that academic studies and their results would be considered as inferior data compared to commercial sponsors on the basis that the same rigorous requirements have not been applied. This in turn may be a disincentive for Academic Institutions to undertake research, if different standards were to be applied, compared to the rest of the research community.

It is also our view that it would be detrimental to exclude the opportunity for the results of academic clinical trials to be referred to in the framework of an application for Market Authorization. In oncology, in particular, due to the well organized network of the clinical research community, many studies sponsored by public scientific organizations have led to the registration of new products (e.g. thalidomide in multiple myeloma), and several new indications for approved products (e.g. rituximab in diffuse large B-cell lymphoma and follicular lymphoma). To exclude such a possibility will be detrimental to both patients and to research in the EU.

A preferred approach would be to unambiguously include Academic studies within the scope of the legislation, whether it is a revised Directive or a Regulation, but with the ability to have differing provisions, according to the context.

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

There is an aspect of the current legislation that, we believe, has not directly been covered in the consultation paper: its detrimental effect on patient's access, especially to cancer clinical studies, via non commercial clinical trials.

A tentative of regulation was introduced by the draft commission guideline: "Draft guidance on 'specific modalities' for non-commercial clinical trials, referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice".

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Although the Clinical Trials Directive has brought more consistency by defining a global framework within which such studies can be handled, there is a need to openly acknowledge their potential added value vs. commercial trials via a clear status. The current draft document does not adequately address this, leading to unsatisfactory status quo and disparate consequences amongst Member States.

The draft guideline states that studies sponsored by a university, a hospital, a public scientific organization, a non profit institution, a patient organization or a researcher should not be part of the development program for a marketing authorization of a medicinal product (section 3.1.1. Characteristics of the sponsor and section 3.1.2 Characteristics of the clinical trial).

In oncology, due to the well organized network of the clinical research community, many studies sponsored by public scientific organizations have led in the past to registration of new products (e.g. thalidomide, multiple myeloma), and several new indications for approved products (e.g. rituximab, diffuse large b-cell lymphoma and follicular lymphoma).

The data from these studies have a high clinical and scientific integrity and as such should not, by principle, be “a priori” excluded for being used within a marketing authorization or new indication application by commercial sponsors. Indeed, it is often difficult to determine upfront, if such studies are to be included in marketing applications. And even if such intent can be determined upfront, the sponsorship of these studies will remain with the cooperative group since the design and conduct of the study is part of the remit of these scientific organizations.

While it is acknowledged that the exclusion of any of these studies from a marketing authorization was not necessarily the intention of the draft guideline, its current wording and lasting draft status leads to high confusion on this aspect, various interpretation amongst Member States and potential detrimental effect on the registration of new treatment options for cancer patients.

Moreover it is a fact that a majority of the non commercial clinical trials requires some level of cooperation with the manufacturers of the Investigational Medicinal Product. An unambiguous acknowledgement of that situation together with an agreed definition of the terms and conditions under which it can be operated would bring transparency and equity for all patients within the EU Community.

In addition, it should be understood that there is a need for differentiation between studies sponsored by academia that could potentially lead to registration versus studies that will not be part of a registration dossier. It is recommended that rather than generally excluding all types of non commercial clinical trials to form part of a marketing

authorization it would be better to outline standards of academic studies that could potentially have a regulatory purpose vs. those that will not.
The above points should be taken into account when revising the legislation and, in the meantime, the draft guideline should be rapidly amended.

Lastly, we would also like to comment on the 2007 "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials".
It is our view that this guidance may not have brought many further clarifications on IMPs vs non-Investigational Medicinal Products (NIMPs) definitions that were not already included in the Clinical Trials Directive. On the other hand it has introduced a number of additional requirements for NIMPs.
From routine Clinical Trials applications filing experience we have found that the understanding of the IMP definition is still inconsistent across all EU member states. Simplification and adaptation is required to establish one set of definitions valid across the EU. These elements should be brought as well in the new legislation and, in the meantime, the "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials" should be rapidly amended.

We look forward to working further with the Commission on shaping the regulatory framework for Human Clinical Trials in the European Union.

Yours sincerely,
Celgene International.

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