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Public consultation on the

ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC PUBLIC CONSULTATION PAPER

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) was founded to promote companies and associations active in research, development, production and distribution of pharmaceutical products and enhance their scientific, technical, economic and legal objectives. EUCOPE provides a platform for discussion for pharmaceutical entrepreneurs and gives its members an early understanding about regulatory developments.

I. General findings

EUCOPE welcomes the efforts of the European Commission to review and enhance the framework for clinical trials. The Commission assessment report provides a realistic description of the current situation in the Member States which is characterized by different requirements and different interpretations even though equivilant situations are concerned.

For EUCOPE, the main topics to be adressed are:

- The need for a **centralized authorization procedure with a single and unique clinical trial application dossier**
- The need for a strict application of current report requirements in accordance with the document "Detailed guidance on the collection, verification and presentation of adverse reaction reports" (ENTR/CT3 April 2006)
- The **need for a harmonized definition** of "substantial amendment", "non-interventional study" and "SUSAR"
- The implementation of appropriate binding Annexes to the revised Directive or an adoption of a Regulation to replace the Directive
- **Supportive instruments and provisions for SMEs** (e.g. with regard to the EMA SME office services and fee reductions)
- Need to increase resources for science and industrial R&D
- Independent monitoring system at the EU level measuring the contribution of research and innovation

II. Remarks on specific Consultation Items

EUCOPE would like to comment especially on the following Consultation Items:

1. Consultation Item 4

With regard to **Consultation Item 4** EUCOPE **supports the proposed option b**: one central authorization of a clinical trial performed by one body for the entire EU ("one-stop-shop" system) **as long as national authorizations remain possible** and are not replaced by the new system. The new system should be additive. The **sponsor should be free to choose** between the national authorization and the central authorization in all cases. However, the national system should be reformed in the respect that we have besides national authorization **a type of decentralized / mutual recognition procedure also for clinical trials**.

An appropriate legal body should be in place where all Member States are represented by rapporteurs, to perform the review process of one single and unique clinical trial application dossier. The authorization would be valid throughout the EU and the clinical trial could be conducted in the entire EU without additional follow-up authorizations needed by additional Member States concerned.

However, this centralized authorization procedure **must not lead to higher cost for sponsors.**

2. Consultation Item 6

Regarding **Consultation Item 6** EUCOPE would like to point to some inconsistencies among Member States concerning the implementation and interpretation of Directive 2001/20/EC:

Substantial amendments:
The definition of 'substantial' should be clarified. Otherwise, considerably different interpretations by sponsors, Competent Authorities (CA) and Ethics Committees (EC) could be the consequence. Also the term 'otherwise significant' does not sufficiently define the type of amendments that are expected to be submitted for approval. Certain Member States have created an additional category of amendment where documents must be submitted "for information". This shows that it is of crucial importance to have a harmonized definition within the EU. The main criterion for establishing whether an amendment is substantial or not is whether it impacts the conduct of the study.

Reporting of SUSARs:
According to the Clinical Trials Directive 2001/20/EC, all relevant information about suspected unexpected serious adverse reactions ("**SUSARs**") have to be reported to the CA and the EC of the Member State concerned. While these provisions seem straightforward, they have led to a multitude of different regimes in the Member States, which has led in turn to multiple reporting of the same SUSAR, lack of reporting and unreliability of the Community data on SUSARs. Moreover, the number of SUSARs received diverges disproportionately amongst some Member States. The different reporting regimes impact the data quality either by duplicate reports being generated or by some reports not being submitted at all, thus reducing the CAs' ability to monitor safety data and thereby address potential risks for clinical trial participants. ECs have neither the capacities nor the competence nor digital means to do 'signal detection' or otherwise systemically identify a change in benefit and risk of the clinical trial. On the contrary, their capacities for protecting the patients are blocked by this administrative burden. Other ways need to be identified to enable ECs to make the required judgements, recognising that CAs already take appropriate action on receipt of such SUSARs. A more efficient approach could therefore be a separation of responsibilities for CAs and ECs.

Non-interventional studies:
The Clinical Trials Directive 2001/20/EC only applies to "interventional trials", not to "non-interventional" studies (NIS). As the Commission report states, the main characteristics of NIS are accepted by all CAs, but the borderline between "interventional trials" and "non-interventional" studies is drawn differently in individual Member States. Moreover, the report underlines that there are divergent interpretations of the term "non-interventional", especially with respect to "no additional diagnostic or monitoring procedure and use of epidemiological methods".

Even concerning the design, there is currently a divergent interpretation at Member State level: Concerning the design, some Member States accept controlled studies without systematic allocation of treatment (e.g. without randomisation) as NIS. Other Member States interpret all designs with comparison of groups even without randomisation as falling under the Clinical Trials Directive.

Therefore, EUCOPE recommends to provide clarification in this respect for example by creating an intermediate category: Low-risk-intervention not falling under the Clinical Trials Directive and no need of authorization by CA.

A clear definition, differentiation and harmonization between Member States is urgently needed.

3. Consultation Items 8 and 12

With regard to **Consultation Item 8** EUCOPE would like to recommend, according to the "Good Manufacturing Practice (GMP) Guidelines, to set out appropriate binding Annexes to a revised Directive to address the abovementioned issues.

Concerning **Consultation Item 12** EUCOPE sees need for the following amendments:

- Centralized review approach as discussed in Consultation Item 4
- Strict separation of review responsibilities between Competent Authorities and Ethical Committees

4. Consultation Item 18

Difficulties for SMEs are in parts similar to those of larger companies. However, there is a higher burden for SMEs due to the increased need for staff for preparation and management of clinical trials as well as for pharmacovigilance tasks, due to the investment required to adapt IT systems to the new safety reporting requirements, and due to an increase of subject indemnity insurance fees. This leads to an overall increase in resources required for the performance of clinical trials in the new regulatory framework which is especially burdensome for SMEs.

Although the "SME Office" at the EMA is already launched to promote innovation and the development of new medicinal products by SMEs EUCOPE recommends **extending the duties of the "SME Office" to support smaller companies also with regard to clinical trials**.

The Commission should also consider implementing a **legal basis for fee reductions** for clinical trials **when SMEs are concerned as sponsors**.

European Federation of Pharmaceutical Entrepreneurs (EUCOPE)

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