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Public consultation on the

ASSESSMENT OF THE FUNCTIONNING 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, www.eucope.org) 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. Via the German Pharmaceutical Industry Association BPI with its 270 member companies and the UK pharma association EMIG with its 140 member companies EUCOPE represents more than 400 member companies, many of them SMEs. In addition, many innovative companies from Sweden, UK, Bulgaria, Italy, Greece, Germany, the Netherlands and Austria are represented on the board of the association.

I. General findings

EUCOPE appreciates 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 equivalent situations are concerned.

Therefore, EUCOPE sees the need for further harmonization on both levels: The level of approval for clinical trials and the decision of Ethic Committees.

Regardless of the various proposals suggested, the objective has to be to align procedures associated with the submission of clinical trials dossiers. This harmonization should reduce submission costs. The requirements for insurance/indemnity may also be simplified and should result in less administrative burden.

For EUCOPE, the main topics to be addressed are:

- The need for a single submission with a subsequent "coordinated assessment procedure" (see 1.3: CAP)

- The single submission should include a binding decision of EMA of whether the file is complete ("one file-principle") before it is submitted to the National Competent Authority (NCA).

- Any harmonization of the approval of clinical trials should go in hand with an increased harmonization on the level of Ethic Committees; one option could be to require one central instance per Member States for Ethical Committee approvals which has to consult with and meet deadlines of the NCAs

- The tacit approval principle as stressed by the Commission has proven as a reliable principle and should thus be maintained to simplify administrative procedure and permit a predictable planning.

- Supportive measures for SMEs such as fee-reductions and the EMA SME office services should be instruments extended and to be used also for clinical trials.

- The need for a harmonized and broadened definition of "non-interventional study".

- An adapted approach regarding rare and ultra rare diseases is necessary since the lower the prevalence, the more cumbersome it is to perform clinical trials in this field.

II. Remarks on specific Consultation Items

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.

EUCOPE agrees with the concept of a single submission because this will reduce administrative burden for the sponsors and give EMA access to all clinical trial dossiers.

We support the idea that submission of a uniform dossier without any additional national requirements to a single portal would greatly reduce the administrative burden (especially for SMEs) connected with national design of submission documentation. The validation of documents by one administrator would ensure that standardized requirements are adopted and published which allows sponsors to save resources.

Currently, many SMEs have to outsource the preparation of documents concerning the clinical trials to contract research organizations (CROs) and to consultants. The different format of dossiers creates administrative burdens for sponsors which could be prevented by a “single submission and one file-concept”. Therefore, it is important that a single submission concept includes a binding decision by EMA for NCAs to whether the file is complete before it is submitted to the NCAs.

In order to create an effective single submission process the following requirements should be met:

- All concerned Member States should have to accept applications in English.

- Standards for the single submission process should be further developed with all stakeholders, agencies and researchers.

- EMA should check whether the file is complete and then submit the dossier to the NCAs for the coordinate assessment in multinational trials.

Furthermore, EUCOPE suggests that EMA should distribute the respective dossiers not only to the NCAs but to the Ethic Committees as well: Hereby, the incorporation of Ethic Committees into the “one file concept” will be promoted.

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

As the Commission rightfully points out a separate assessment would insufficiently address the issues set out above. The difficulties created by independent assessments of multinational trials would remain.

EUCOPE agrees with the Commission appraisal. Conducting separate assessments will continue to lead to potential different outcomes as a convergence of regulatory and ethical standards will not be facilitated across Europe. Different assessment processes may be also questioned from an equality perspective since it would lead to unequal access to clinical trials, depending where patients live.

1.2. Single submission with subsequent central assessment

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

The Commission sets out that a central assessment is not appropriate for clinical trials approval and would not be workable in practice.

EUCOPE favors a single submission with a 'coordinated assessment procedure' (CAP, see 1.3) and not a central assessment (1.2). However, the concept of a centralized assessment would be worth considering in the future as an alternative, if the Commission would provide the stakeholders with further information on the scope and conditions of this assessment.

Very few clinical trials are rolled out in more than five or six Member States. A closely coordinated virtual assessment procedure supported by a very good IT infrastructure and involving the relevant country experts may provide a pragmatic and fast solution.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

1.3.1. Scope of the CAP

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

The catalogue is not complete.

The acceptability of the clinical trial in view of all anticipated benefits (point 1.3.1 a) compared to risks and inconveniences for trial subjects should take into account the life-saving potential of the therapy being investigated, notably for conditions with ultra low-prevalence for which no alternative treatment exists. An adjusted approach regarding rare and ultra rare diseases is necessary since the lower the prevalence, the more cumbersome it is to perform clinical trials in this field.

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

EUCOPE agrees that aspects under a) should be included in the scope of the CAP. In addition, it is crucial to implement ethical aspects - listed under b) - into the scope of the CAP as well.

At present, the ethical review - being done on a local level - is very different from one Member State to another. This is problematic as the approach leads to an unequal access

to clinical trials within the EU. In this regard, countries such as Belgium and UK just have initiated better coordination at national level but are far from harmonization.

We urgently propose that the coordination of the national and local ethical aspects is also managed via the central secretariat to ensure an overall coherent process which is completed within the legal timelines. Currently, the ethical review by local country Ethical Committee is a complex process and very different from one country to another.

1.3.2. Disagreement with the assessment report

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

According to EUCOPE, the opt out-approach is preferable. The opt-out should take place only and immediately after the sponsor has withdrawn the application for this Member State. Otherwise, one Member State could block the CAP and delay timelines.

Before an opt-out takes place, the concerned Member States should consult with the sponsor and the other NCAs with the objective to reach a common decision on public health and patient safety. Suitable appeal mechanisms should be created.

1.3.3. Mandatory/optional use

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

The CAP (1.3.) should be optional for all multi-country clinical trials like the current voluntary harmonization procedure (VHP). The Single submission with separate assessment (1.1.) could be an alternative and could be especially suited for clinical trial in only a few Member States. Also in case of major disagreements and several opt outs of Member States the separate assessment would be an option.

This optional approach permits to obtain a simple and harmonized system and to set similar standards within the EU.

1.3.4. Tacit approval and timelines

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

The appraisal of pre-assessment is considered as a good proposal. A system similar to that existing currently in the UK with a table or Q&A defining the criteria would be an interesting option. However, if the pre-assessment step in general adds to the overall

timeline for all clinical trial assessments, there may be limited benefit in having such step to identify certain type A trial with potential shorter timeline.

A clinical trial conducted as phase IV study, i.e. within the authorized indication, population, dosage and treatment duration usually poses only “minimal risk” to the safety of the trial subject. It needs, however, to be more clearly defined what the Commission considers as “the interventions in the trial do not pose more than insignificant additional risk to the safety compared to normal clinical practice in a MS concerned”. Usually, phase IV studies require not only randomization but at least also some additional blood samples. Is this considered as “insignificant additional risk”? It has to be defined who will decide on the classification of a study as a type A trial.

Tacit approval is supported very much since it allows a predictable development timeline and planning. As the Commission sets out the instrument has been implemented in Directive 2001/20/EC. EUCOPE strongly supports a tacit approval, since it has proven as a successful and reliable instrument. Therefore, we would urge the Commission to remain the current approach under directive 2001/20/EC and extend the tacit approval concept to the CAP. If the tacit approval concept is possible even today for single assessments by NCAs it should be possible to implement it as well for a coordinated assessment of several NCAs under the CAP. Timelines existing in the current version of Directive 2001/20/EC should remain the same for both NCAs (Art. 9 para. 4) and Ethic Committees (Art. 6 para. 5) or should be shortened in case of specific needs or circumstances.

Timelines (point 1.3.4) should for example be adapted to take into consideration the life-threatening character of a disease when no other treatment option exists. This is particularly crucial for patients with rare and ultra-rare diseases, considering that it often takes time to diagnose them properly (or for fastly-progressing diseases such as MoCD).

2. BETTER ADAPTATION 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

2.1.1. Enlarging the definition of ‘non-interventional’ trials

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

EUCOPE would welcome any efforts limiting the scope of the Clinical Trial Directive possibly through a wider definition of non-interventional trials.

We also see the need for further harmonization regarding non-interventional trials as long as this is decreasing administrative burden. At present, non interventional studies (NIS)

are regulated on national level and regulation differs very much from one country to another. Harmonized requirements in the EU are preferable to better compare the results and to make an EU wide compliance oversight possible. The definition must be consistent amongst Member States, particularly since the NIS will be increasingly used for health technology assessments (HTAs).

However, we would like to emphasize two very important aspects in this regard:

1. Under any harmonized approach, non-interventional trials should not have to fulfill the criteria of the Clinical Trial Directive. According to the Directive clinical trials have to be conducted according to the Good Clinical Practice (GCP). GCP is mandatory for all interventional studies, even if they impose only "insignificant additional risk" to trial subjects. In this context we refer to our comments in consultation item 8 (type A trial). In addition, NIS are characterized by the fact that they are in agreement with the every-day practice. Therefore, it is not necessary to subject them to rules as rigid as for explicit clinical trials.

2. For the reasons mentioned above any kind of authorization requirement and GCP requirements should be rejected for NIS.

Finally, EUCOPE appreciates that the European Commission recognizes the particular difficulty to carry research on rare diseases (see point 2): The lower the prevalence of these diseases the more cumbersome it is to perform clinical trials. Therefore, these diseases require an adapted approach for orphan and ultra orphan medicinal products.

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

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

EUCOPE fully agrees and sees no need to exclude academic/non-commercial sponsors from the scope of the CT directive due to the fact that safety needs to be ensured in all cases. Rather than excluding non-commerial clinical trials / sponsors, it would be better to come up with harmonized and proportionate requirements for clinical trials, which would apply independently of the nature of the sponsor ("commercial" or "academic/non-commercial").

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.

EUCOPE generally agrees that more detailed and binding provisions should be enshrined in EU legislation if this helps achieving greater harmonization of these aspects at local level. Specific attention should also be given to synchronizing the timelines for national implementation of such rules across all EU countries. However, more specific information on the content of annexes is required. In addition, it needs to be discussed whether delegated acts seem to be the appropriate instrument for this important aspect. Basic requirements should be set out in the directive.

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

EUCOPE proposes the following key aspects on which more detailed rules are useful:

- A clear and EU-wide definition of "risk-based-approach"
- Documents should be submitted to Ethic Committes and NCAs through a single portal
- More detailed rules on working procedures of Ethical Committees and NCAs
- More detailed rules on studies for specific patient populations (rare diseases, children, intensive care or emergency patients)
- More detailed rules on insurance requirements and Data protection in clinical trials

The most important aspect would be to have clear working procedures for Ethics Committees.

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.

EUCOPE agrees that this approach would help to simplify the rules for medicinal products used in the context of a clinical trial. It is, however, important to restrict the necessary documentation to an amount adequate for the use in clinical trials, i.e. the dossier for AMPs should be concise.

However, a notion of "auxiliary medicinal product" might rather be confusing than clarifying: The term "non-IMPs" or "NIMPs" which is already used in guidelines seems to be more appropriate. Examples for "NIMPs" are medicinal products which are used as challenge agents, rescue medication, and background treatment. In any case clear

definitions have to be set out in order to distinguish between different regulatory requirements.

2.4. Insurance/indemnisation

2.4.1. The issue

2.4.2. Policy options

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

According to directive 2001/20/EC, the liability of the investigator or sponsor for possible injury or death of the trial subject has to be covered by insurance or indemnity. A risk-based approach should be implemented, i. e. in connection with Type A trials (consultation item No. 8). Clinical trials in Phase IV, which are conducted in the authorized indication, should be excluded from insurance / indemnity. Also the sponsors should not be obliged to consult the respective Ethic Committees as this would delay the study initiation.

2.5. Single sponsor

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

EUCOPE agrees with the appraisal (option 1). In order to achieve a precise distinction of responsibility within a clinical trial, the concept of single sponsorship is to be maintained. Any ”multiple sponsorship” might lead to conflicts regarding different responsibilities for quality obligations or divergent approaches in case of adverse events between sponsors.

2.6. Emergency clinical trials

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

EUCOPE agrees with the appraisal that the informed consent and the information from the investigator may - under specific conditions - take place during or after the clinical trial, in line with internationally agreed texts. In addition, NCAs should pay specific attention to those conditions / trials and the definition of the legal representative has to be clear in this respect.

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.

EUCOPE agrees with the Commission's intention to allow for more flexibility concerning the acceptance of data derived from clinical trials in third countries, especially in the case of rare and ultra rare diseases as it is particularly difficult to find patients participating in trials or studies.

Concerning the registration and results posting of clinical trials EUCOPE does not encourage requiring an additional registration of third country trials within in the EudraCT database. Publication of third countries trials in the EudraCT database could be an alternative only if trials are not already included in another recognised public registry.

Since there are different databases existing concerning the registration of clinical trials such as initiated by IFPMA and the WHO, a mandatory registration into the EudraCT database would present further complexity and administrative burden demanding additional resources without additional public health benefit.

With regard to the risk of increasing flood of data than necessary in different databases, double registration and differing requirements should be prevented. In fact, transatlantic harmonization of several databases may be the objective.

European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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