EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

POSITION PAPER (REV.01)

EGA CONTRIBUTION TO THE EC PUBLIC CONSULTATION ON THE CONCEPT PAPER ON THE REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

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The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

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1. EXECUTIVE SUMMARY

We concur with a large part of the EC preliminary appraisals put forward for public consultation and welcome the opportunity given to industry to comment on those.
We believe that a single submission would greatly reduce the administrative work linked to the clinical trial application. We also support the proposal that any subsequent applications by the same sponsor would refer to the information previously submitted.
We do concur with the EC that a separate assessment by concerned Member States (MSs) would insufficiently address the need for administrative relief and the need to avoid duplication of assessment work for a single clinical trial application.
The EGA acknowledges the EC preliminary appraisal highlighting the difficulties and complexities of having a central assessment for clinical trial applications and their subsequent substantial amendments. However, we would like to point out that a central assessment could remain an option for clinical trial applications meeting a number of eligibility criteria.
We definitely reckon that aspects relating to ethical issues or local expertise are more complex to handle at a European or central level however rather than excluding them upfront we believe that certain aspects could be identified as suitable for inclusion in the scope of the CAP.
We welcome the three options proposed by the EC in order to solve and settle potential disagreement with the assessment report. We would favour the option where MSs conclude on a given concern based on majority voting.
We support the EC proposal that the CAP should remain an optional assessment process making a parallel to today's situation for Marketing Authorisation Procedures where National procedures co-exist with MRP/DCP and Centralised procedures.
We strongly support the inclusion of the notion of clinical trial "risk" and the EC preliminary appraisal that a simpler, clearer and streamlined set of EU -wide risk-adapted rules is a desirable outcome in the future legislative proposal amending the Clinical Trials Directive.
We would ideally prefer the removal of insurance/indemnisation requirements for low-risk clinical trials however national laws as well as the Declaration of Helsinki require either insurance or provisions for compensating harmed subjects. Therefore the EGA would support the EC policy option 2: Optional indemnisation by Member States.
We support the EC proposal in relation to transparency. We would however support the introduction of an EU waiver for bioavailability and bioequivalence studies on the model of the current planned revision of the German legislation for the requirement to register clinical studies.

2. Cooperation in assessing and following up applications for clinical trials Single submission with separate assessment

- Consultation item no. 1 - Single submission reduces administrative burden

EGA Comments:
We do concur with the EC preliminary appraisal that a single submission would greatly reduce the administrative work linked to the clinical trial application.
We also support the proposal that any subsequent applications by the same sponsor would refer to the information previously submitted.
The potential administrative relief of such approach is deemed substantial, from an industry and, to some extent, also from a regulators' perspective.

- Consultation item no. 2 - Independent assessment does not reduce complexity

EGA Comments:
We do concur with the EC preliminary appraisal that a separate assessment by concerned Member States (MSs) would insufficiently address the need for administrative relief and avoidance of duplication of assessment work for a single clinical trial application.
We believe this would not help addressing today's sub-optimal authorities' resources allocation in the field of clinical trial applications.

2.2. Single submission with subsequent central assessment

- Consultation item no. 3 – Central assessment appropriateness for clinical trials

EGA Comments:
The EGA acknowledges the EC preliminary appraisal highlighting the difficulties and complexities of having a central assessment for clinical trial applications and their subsequent substantial amendments.
However, we would like to point out that a central assessment could remain an option for clinical trial applications meeting a number of eligibility criteria.
These would address the various concerns such as highlighted in the preliminary appraisal and contribute to limit the overall number of trials qualifying for such assessment.
In addition, the argumentation related to the cost of creating a central structure in the preliminary appraisal seems to be valid only partially. On the one hand, it is true that a new central infrastructure would have to be established. On the other hand, the national workload would be significantly reduced with the overall advantage of reduced duplication of work.

2.3. Single submission with subsequent coordinated assessment procedure ('CAP')

- Consultation item no. 4 – Scope of the CAP

EGA Comments:
We believe the catalogue of aspects to consider within the scope of a clinical trial application as presented in the EC consultation document is complete and comprehensive.

- Consultation item no. 5 – Scope / risk benefit assessment

EGA Comments:
We support the inclusion of all aspects under point a) as presented in the EC consultation document in the scope of the CAP.
We definitely reckon that aspects relating to ethical issues or local expertise are more complex to handle at a European or central level however rather than excluding them upfront we believe that certain aspects could be identified as suitable for inclusion in the scope of the CAP. For example, ethical aspects such as completeness and adequateness of the information submitted to obtain informed consent or arrangements for the recruitment of trial subjects might as well be assessed centrally.

- Consultation item no. 6 – Disagreement with the assessment report

EGA Comments:
We welcome the three options proposed by the EC in order to solve and settle potential disagreement with the assessment report.
In an order of preference, we would favour
***option 2, where MSs conclude on a concern based on majority voting**, then
*option 1, where a disagreeing MS could be allowed to opt out if justified on the basis of Serious Risk to Public Health (SRPH) or safety to participants, and finally
*option 3, where the EC or the EMA would take a decision.
From our existing experience with the use of the SRPH justification in the context of Bioequivalence assessment, the variability of interpretation of this concept led to a high unpredictability of data packages which is certainly desirable to avoid in the process of streamlining the clinical trial applications as proposed in option 1.
Regarding option 3, we are even more concerned than with option 1 that this procedure would significantly prolong timelines for approval of a clinical study. **Long lead times are already a major disadvantage for performance of clinical trials in the EU in the current legal framework and a primary objective of the CT Directive legislative update would be to bring EU lead times in line with other key countries as far as clinical trial performance is concerned.**

- Consultation item no. 7 – Mandatory / optional use

EGA Comments:
We support the EC proposal number 3 as a preferred approach: the CAP should remain an optional assessment process making a parallel to today's situation for Marketing Authorisation Procedures where National procedures co-exist with MRP/DCP and Centralised procedures. Having a 'twin engine' system usually provides for flexibility. It would allow a smooth 'learning curve' for CAP, for both industry and authorities, while maintaining the current system which is well known and therefore limit the potential bottleneck of having 100% clinical trial applications (eligible for CAP according to final scope definition) and their subsequent amendments mandatorily via the CAP.

- Consultation item no. 8 – Tacit approval and timelines / pre-assessment and identification of low risk trials

EGA Comments:

We strongly support the inclusion of the notion of clinical trial "risk" in the future legislative proposal amending the Clinical Trials Directive.

We particularly welcome that any clinical trial potentially identified as 'low risk' (i.e. class A) trial would be eligible for shorter timelines and highly focused assessment. We encourage a re-definition of timelines for approval prior to study initiation for such low risk clinical trials (e.g. pharmacokinetic studies in healthy subjects supporting the registration of generic medicinal products (known API, same strength) to 10 or maximum 15 days in order to be competitive against those provided in Canada.

Regarding the EC proposal to have a pre-assessment in order to identify those trials being Class A trials, we believe that this would be feasible however the timelines associated with such pre-assessment should be clearly defined.

In certain cases, such as for clinical trials aimed at supporting the registration of generic medicines, the pre-assessment should be automatic. A suggestion could be for it to be part of the clinical application form in the form of 'self-assessment' either as an 'applicant declaration' or through the ticking of boxes. It would be unreasonable to allocate MSs resources to the pre-assessment of straightforward bioequivalence studies which by essence pose only minimal risks to the safety of the trial subject compared to normal clinical practice.

In addition, biosimilar medicines can also be defined as ones with known safety profile and we believe the relevant clinical studies programme would qualify as lower risk clinical trials.

We would recommend that a clear definition of "low risk" is included as part of the directive or as an annex so that a harmonious interpretation is promoted among different member states.

Beyond pre-study protocol approval timelines, we believe the documentation requirements applicable to low risk clinical trials should be redefined so as to limit administrative burden to the minimum necessary.

3. Better adaptation to practical requirements and more harmonized, risk-adapted approach to the procedural aspects of clinical trials

3.1. Limiting the scope of the Clinical Trials Directive

- Consultation item no. 9 – Enlarging the definition of 'non-interventional' trials

EGA Comments:

We support the EC preliminary appraisal that rather than expanding the definition on 'non-interventional' trials in order to avoid those trials where consensus among EU MSs is difficult, the overall approach to the future legislative proposal should be to foster upfront discussions and agreements on harmonised concepts and proportionate requirements for all clinical trials.

- Consultation item no. 10 – Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

EGA Comments:
Same as above.
We support the EC preliminary appraisal that excluding more trials from the scope of the Directive based on the nature of the sponsor would be counter-productive in the long-run.
We support the EC appraisal that the preferred approach to the future legislative proposal should all encompassing and should foster upfront discussions and agreements on harmonised concepts and proportionate requirements between MSs.

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

- Consultation item no. 11 – Risk-adaptation simplifies, clarifies and streamlines the rules for clinical trials

EGA Comments:
We support the EC preliminary appraisal that a simpler, clearer and streamlined set of EU -wide risk-adapted rules is a desirable outcome of the future legislative proposal.
Defining these rules as part of the Directive it-self (ie, Annexes) would definitely enhance the level of harmonisation between MSs however, we can anticipate that in the event these annexes would need to be amended or updated, the legislative process to do so would be quite lengthy.

- Consultation item no. 12 – Risk-adaptation / additional key aspects to consider

EGA Comments:
We are of the opinion that the aspects listed in the EC preliminary appraisal duly cover all key items to be considered.

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

- Consultation item no. 13 – Combined approach

EGA Comments:
The EC preliminary appraisal consisting in a combined approach (definitions of IMP and auxiliary product and disctinct & proportionate regulatory regime) is welcome.

3.4. Insurance/indemnisation

- Consultation item no. 14 – Preferred policy option

EGA Comments:
We would ideally prefer EC policy option 1: removal of insurance/indemnisation requirements for low-risk (Class A) clinical trials however national laws as well as the Declaration of Helsinki require either insurance or provisions for compensating harmed subjects. Therefore the EGA would support the EC policy option 2: Optional indemnisation by Member States.

3.5. Single Sponsor

- Consultation item no. 15 – Single sponsor concept

EGA Comments:
We support the EC preliminary appraisal however we recommend that the future legislative proposal is very detailed about this aspect in order to limit interpretation and guarantee a predictable outcome for applicants.

3.6. Emergency clinical trials

- Consultation item no. 16 – Proposed approach

EGA Comments:
The EC preliminary appraisal seems reasonable and we generally support alignment on internationally agreed regulatory concepts.

4. Ensuring Compliance with Good Clinical Practices in Clinical Trials Performed in Third Countries

- Consultation item no. 17 – Legal change / capacity building in 3rd countries / transparency in EudraCT & EudraPharm

EGA Comments:
We support the EC preliminary appraisal that both codifying the provision in point 2.7.2.4 of the detailed guidance CT-1 and supporting capacity building in 3rd countries would strengthen the EMA actions. We also support the EC proposal in relation to transparency and registration of clinical trials to be used for marketing authorisation purposes of respective medicinal products in the EU.
We would however support the introduction of an EU waiver for bioavailability and bioequivalence studies on the model of the current planned revision of the German legislation for the requirement to register clinical studies.

5. Figures and data

- Consultation item no. 18 – Additional Quantifiable information

EGA Comments:
We have no further comments. The Annex appears to contain a lot of useful figures and information.
We would see added value in keeping this Annex as suitable for a publication as a standalone document which could be updated on an annual basis.