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Stellungnahme

Public Consultation
on the Revision of the "Clinical Trials Directive" 2001/20/EC

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION
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European Commission

Comments of the German Pharmaceutical Industry Association, BPI
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BPI appreciates the efforts of the European Commission to enhance the framework for clinical trials which is currently characterized by different requirements and different interpretations in the Member States even though equivalent situations are concerned.

With over 50 years of experience in drug research, development, authorisation, manufacturing and marketing, German Pharmaceutical Industry Association (BPI – Bundesverband der Pharmazeutischen Industrie e. V.) covers the wide range of pharmaceutical industry activities at national and international levels. There are more than 260 companies with more than 72,000 employees organized in the BPI: Classic pharmaceutical companies, biotechnology, phytopharmacy and homeopathy/ anthroposophy as well as pharma service providers. BPI represents both innovative pharma- and biotech-companies and companies with a small generic product portfolio. The diversified structure of BPI is also reflected by the fact that multinational companies as well as small and medium-sized enterprises are members of the association. The pharmaceutical industry employs approx. 643.000 people in the 27 EU-Member States. BPI, therefore, represents more than 11 % of staff working in the pharmaceutical industry in the European Union.

I. General Comments

Regardless of the various proposals suggested, the objective has to be to align procedures associated with the submission of clinical trials dossiers to harmonise and simplify the requirements as well as to reduce submission costs. The requirements for insurance/indemnity may also be simplified and should result in less administrative burden. BPI sees the need for further harmonization on both levels: The level of approval for clinical trials and the decision of Ethic Commitees.

II. Comments on specific Consultation Items

Consultation Item	BPI Comments
1	**BPI agrees with the appraisal of a single submission through a single web-portal.** It is appropriate as it will considerably reduce the workload in submitting documentation where authorities in several Member States are to be addressed.

	The electronic submission of one uniform dossier without any additional national requirements to a single EU-Webportal would greatly reduce the administrative burden (especially for SMEs). The only accepted language needs to be English. The validation of documents following one administrative rule would ensure that standardised requirements are adopted and published.
2 and 3	**BPI agrees that both, the appraisal of the separate assessments as well as the appraisal of a central assessment raises some concerns:** **1.2. Single submission with subsequent central assessment** A central assessment is appropriate for scientific aspects of trials. The concept paper suggests that it is not workable due to ethical, national and local perspectives. Ethical considerations should not be a matter of consideration for the CA, this should be the responsibility of the EC. The role of the EC is note addressed in this part of the proposal. (In any case, while in practice EC matters are a matter of national practice, ideally they should be independent of the patient's location.) • If ICFs or financial matters are reviewed by CAs then this would need to be reviewed nationally. • It is agreed that as there are about 1200 multinational trials per year, a central review would represent an impractical workload, in particular once substantial amendments and annual report reviews are considered. It is also agreed that it is unnecessary for non-concerned MS to review such applications especially given the statement that very few trials involve more than 5 or 6 MS. • The proposal suggests that the frequency of committee meetings together with associated infrastructure would make the burden of fees unacceptably high for non-commercial sponsors. While this is no doubt correct, it should also be borne in mind commercial sponsors should not be viewed as having access to unlimited funds. • This procedure is described as reflecting the centralised procedure however no details are provided; it is not stated whether an assessment report would be prepared by a rapporteur, to be reviewed by all MS or if another mechanism would apply**.** In accordance with other procedures in marketing authorisation or pharmacovigilance, a special committee could be established, where the members and alternates are nominated by the European Union Member States. Assessments conducted by this Committee needs to be based on purely scientific criteria and determine whether or not the clinical trial concerned meet the necessary requirements (in accordance with EU legislation, particularly Directive 2001/20/EC), even concerning the benefit-risk assessment.

	Even concerning Complementary and Alternative Medicines (CAM) the proposed alternative of a central assessment would fail to deliver a fair and proper assessment mechanism for studies involving pharmaceutical products within the scope of anthroposophical medicine and, indeed, for studies involving complementary medicine more generally. Separate assessment permits those Member States with the appropriate knowledge and experience specifically to be addressed, thus permitting informed and objective assessment of the information submitted. From country to country varying ethical standards are not helpful to support acceptance of clinical trials – by the patient or by the investigator. Furthermore the basic ethical conditions should be consistent – otherwise we might end up with "high ethical standard countries" (US/EU) and „low ethical standard countries" (e.g. how to get an informed consent form properly in India?). **1.3. Single submission with a subsequent 'coordinated assessment procedure'** BPI agrees with the 'coordinated assessment procedure' (CAP) performed by the Member States concerned. Thus, the CAP is the assessment of choice. All other criteria like ethical aspects and local aspects should be task of the ECs. It may be useful to have a special rule in place for CAM mainly due to the special scientific questions.
4	**The catalogue is not complete.** The list under a) is covering not only tasks of the competent authorities (CA) of the MS but also tasks currently performed by Ethics Committees (EC) (i. e. aspects regarding risk-benefit-assessment on the clinical trial protocol). Assuming that CAP will involve CAs of MS as well as the ECs, the list under a) has to be changed accordingly. The CAP should include assessment of compliance regarding the requirements for the Investigational Product including manufacturing, importation, labeling as well as Investigators Brochure. Regarding the later acceptability of a trial in a marketing authorization procedure also the following aspects could be part of CAP (questions that are usually asked within Scientific Advice Procedures), e. g. • choice of control group, • choice of primary and secondary variables, • choice of sample size and planned statistics, • choice of treatment dosage/duration / study duration. All above mentioned aspects are not to be solely assessed regarding „risk-benefit" but regarding acceptability for market authorization. Other missing aspects in the list are compliance with GCP

	• handling of blood samples etc., • analysis and statistical methods, • compliance with data protection.
5	**BPI does not agree.** As clearly communicated in the stakeholder meeting it is intended that there should be no „dualism“ of CAs and ECs anymore. Thus, it is aimed that through the single EU portal documents for both CAs and ECs are submitted and it is aimed in obtaining a single decision per MS. The procedure how ECs will be included in the decision finding process, however, is not clear. This uncertainty of the procedure does not allow the statement that only the catalogue under 1.3.1a but not 1.3.1b and 1.3.2c should be included in the CAP assessment. Currently, the ethical review by local country Ethical Committee is a complex process and very different from one country to another. This is problematic as the approach leads to an unequal access to clinical trials within the EU. We urgently propose a central coordination of ethical aspects to ensure an overall coherent process which is completed within the legal timelines.
6	**BPI agrees** Individual Member State should be allowed to opt out.
7	**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.
8	**Pre-assessment** 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. BPI 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 lifethreatening 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 PNH or MoCD).
9	**Whether or not the definition of non-interventional trial is changed, the interpretation needs to be consistent amongst MS.** BPI 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, BPI 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.
10	**GCP requirements should apply to all clinical interventional trials independently who is acting as the sponsor of the trial. Even the level of patient protection requirements should be independent from the following use of data gathered in the trial.** However, it would seem reasonable that the patients who volunteer for trials are entitled to expect that the robustness of the resulting data is independent of its final use e.g. commercial vs publication. • Regulation of interventional trials should be undertaken on a risk based approach as described in Section 1.3.4 above. We are critical of any suggestion that different regulatory requirements should apply to „non-commercial" as distinct from „commercial" studies. GCP is in place to protect the safety of patients and to ensure that data are collected in accordance with scientifically valid methodologies. Every sponsor is obliged to ensure that these standards are achieved. No „light-version" of clinical trial should be allowed.
11	**BPI 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.
12	**This approach is very pragmatic and no crucial aspects are missing.** It is recommended that the contents of the guideline defining types of non-IMP and non-IMPD content could also be included as an Annex to the legislation. • Consideration might be given to converting Annex 13 of the GMP guidelines to an Annex of the CT Directive however this is less of a priority. • As more flexibility is required on CTA content, the guidelines on IMPD content (chemical and biological actives) should remain as guidelines.

13	**BPI agrees with the appraisal given for the new definition of auxiliary medicinal products for this helps to deal with this important phenomenon in a clarified manner.** 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.
14	**As to indemnisation and liability no approach should be deemed fair that leaves trial participants without an insurance and leaves the sponsor or investigator with the necessity for indemnisation at the same time.** A risk-based approach is deemed adequate. However, insurance fees should be made adequate to the risk envolved. The definition of the amount of payments should be adapted to the approach outlined for the preassessment procedure. While the concept of risk-based need for insurance/indemnity is reasonable, very clear requirements on the number of categories, the type of study that falls into a given category, the requirement for insurance/indemnity for a given category, etc. Sponsors need to know the study specific category well in advance of submission to a CA or EC without the need for consultation with the EC, as this would delay study initiation. • If the system operates on a country specific basis, this implies that MS would individually determine the level of risk associated with a given trial and thus potentially result in divergent assessments. A pan-EU risk assessment should be undertaken, as outlined in Section 1.3.4. • Whilst the proposal to exempt drugs which are authorised as per the various EU Directives is unexceptional, especially if they are used only as per the authorisation, other parts of the definition are rather vague, and there are no precise definitions for the following: 1. ‘standard treatment in a Member State concerned’, 2. ‘insignificant additional risk’, 3. ‘normal clinical practice’.
15	**BPI 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.
16	**BPI 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.

	The CT Directive currently contains guidance on informed consent for incapacitated patients. While emergency trials are not specifically addressed, an emergency arises when a normally able adult is rendered incapacitated or when the legal representative/parent of a normally incapacitated adult/child is unavailable in a time critical situation. As such, it is appropriate that specific text on emergencies be viewed as an extension of the existing text on children/incapacitated adults (Articles 4 and 5), as appropriate.
17	**BPI 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.** It is honorable that the EU-commission offers support for countries outside the EU. This approach is recommended to respect different cultures and their approaches. In this context it seems far-fetched to demand trials carried out in third countries to be registered in a mere EU-based register. While it is commendable to support capacity building in third countries it would not be feasible to introduce this as legally binding. As such it is not clear where this statement would appear in the legislation, if anywhere e.g. introductory „whereas" of the CT Directive. Publication of third countries trials in the EudraCT database could be an alternative where trials are not already included in another recognised public registry.
18	**The concept of risk assessment is raised with respect to different aspects of the study.** The nature of the risk may be the same in some of those assessments (such as level of intervention affecting review time and also insurance needs) but not in others (product quality related). If one or more assessment of different types of risk is required these should be undertaken transparent and EU-wide.