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Name of organisation or individual :	pharma.be
Role of the commenter :	Belgium Pharmaceutical industry association – originator products

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1.1. Single submission with separate assessment (p2)	We fully agree that submission of a uniform dossier without any additional national requirements to a single portal would greatly reduce the administrative workload connected with national tailoring of submission documentation. The validation of documents by one administrator would ensure that standardized requirements are adopted and published which allow sponsors to achieve a "first-time-right" submission and save resources. Such approach requires that sufficient funding for human resources and infrastructure from EU or national level is made available to develop the appropriate submission infrastructure as a basis for enhanced collaboration. In addition, we recommend that the standards for the submission process are developed in an inclusive process with all stakeholders, ie. agencies, IRB, researchers etc., so that the needs of all parties is reflected. Eventually, the submission is only one step in the process, and other steps should be streamlined as well (for more see below). ERC review must stay running in parallel. <u>Questions:</u> Will not participating countries have the right for consultation?

	Will a tracking system be developed to allow the sponsor to follow-up the file (like the Eudralink system) ? How would be set up the communication process between the local sponsor and local MOH ? How would be set up the single submission to IRB ? Would the fees stay proportional to the purpose (middle-small size company and studies with limited number of study sites). Will Phase I be part of the process, what could negatively impact fees and timeline; would Belgium/EU remain competitive ? Belgium benefit: would keep the advantage in fast time review and stay competitive for early phase research.
1.2. Single submission with subsequent central assessment (p3)	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. However, any centralised assessment should also reflect local conditions (infrastructure, healthcare system etc.); therefore certain flexibility may be necessary. In addition, opportunities for Regulator Peer discussions and capacity building may be lost. We agree that a full Committee structure and its high cost and limited flexible meeting schedules would make the review process very cumbersome with an inflexible time schedule. In addition, the assessment of trials which are conducted in only 1 or 2 countries, such as Phase I studies may be slowed down. Imposing an EU level Regulatory system on authorizations that are only relevant for a limited number of participating countries would unnecessarily take resources from non participating countries. Such Committee would only make sense if all Member States are concerned by the assessment process. Specifically for trials that are conducting in a smaller number of Member States, this process may be too rigid and slow. The approval would need to be followed by a Commission Decision translated into 23 languages, which is unnecessary in most cases, as trials will seldom involve every single member state in the EU. 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	1.3.1. Scope of the CAP (p3) We agree that aspects under a) should be included in the CAP. However, we would suggest that the co-ordination of the national and local ethical aspects is also managed

assessment procedure' (p3)	via the central secretariat to ensure an overall coherent process which is completed within the legal timelines. In the long run, standards for CT in the EU should be on the same level, and a more flexible approach would enhance common standards where feasible. Currently, the ethical review by local country ERC is a complex process and very different from one country to another. A better co-ordination at national level has just been initiated (such as UK and Belgium). In addition, equity considerations should also be included in ethical assessments in order to ensure equal access to CT in the EU. However, this needs to be co-ordinated at a central level. *1.3.2. Disagreement with the assessment report (p6)* "Opt out" is the preferred option and it would be interesting to have an "Opt in" option if another MS wants to join without any further assessment. Considering that CAP would only be initiated for multi-country trials, in case or disagreements, we would prefer that the concerned Member States could raise justified serious risk to public health issues, and opt out in case of major disagreements. This specifically is related to ethical concerns and differences. Member states must have the opportunity to raise their justified concerns for a peer discussion. The concerned Member States should try to arrive at a common decision on public health and patient safety throughout the EU whenever possible. It is important, that the process for solving Member State disagreements does not prolong the legal timelines. Adequate appeal mechanisms should be foreseen. *1.3.3. Mandatory/optional use (p6)* The CAP should be optional for all multi-country clinical trials. It is a good approach to achieve a simple and harmonized system and set similar standards across the EU. For single site or single country trials, specifically Phase I studies, faster procedures facilitated by the national agency concerned should be adopted. Nevertheless, the same principles and requirements should apply to all clinical trials conducted on EU territory. Questions: can we ensure the system will keep a parallel evaluation between local and ethical review. **Belgium benefit**: opportunity to keep studies locally if Belgium is chosen as reporting member states (provided enough resources are allocated at the agency level!). *1.3.4. Tacit approval and timelines(p7)* A standard informed consent and investigator contract should be developed. 1.3.4. This option is fine provided stringent timelines for CAP and MS assessment are provided.

1.4. Do you think such a pre-assessment is workable in practice?	Pre-assessment by the sponsor may be a good proposal. A system similar to that currently in operation 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 trials with potential shorter timeline. Tacit approval in case the legal timeline has passed is supported to allow a predictable development timeline and planning.
2.1. Limiting the scope of the Clinical Trials Directive (p8-9)	2.1.1. Enlarging the definition of 'non-interventional' trials (9). According to the recently adopted Pharmacovigilance legislation (amending Directive 2001/83/EC), Chapter 4, protocols for all non-interventional post-authorisation safety studies are reviewed and approved by the new Pharmacovigilance and Risk Assessment Committee. As such a part of non-interventional studies are already conducted under regulatory oversight. This new legal requirements need to be considered when developing a comprehensive system without any potential for duplication. Any potential for conflicting guidance, as conflict with existing ISPE guidance, Volume 9A, and still to be written "Good Pharmacovigilance Practice" is quite possible and should be taken into account. Currently, non interventional studies are locally regulated, but regulation is very different from one country to the others; Harmonization of the requirements in EU are certainly useful to better compare the results and enable EU wide compliance oversight. However, we believe that such harmonization efforts should perhaps be done through a different legal instrument and not embedded into the Clinical Trials legislation. 2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors'from the scope of the Clinical Trials Directive (10). Academic/non-commercial sponsors should be included in the scope of the Clinical Trials Directive.
2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting (p10)	We agree that more detailed rules enshrined in EU legislation would help 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. Are there other key aspects on which more detailed rules are needed? Please consider writing EU –wide rules on the definition of "risk-based-approach". In addition, local guidance exists in several therapeutics areas (e.g. Diabetes) which conflicts with international guidance usually applied for global protocol design. EU-wide guidance related to specific clinical trials design aspects should be linked to the relevant regulatory development guidance governed by

	the CHMP/EMA.
2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'	Auxiliary medicinal products could be defined by the intention of usage as well as the mode of administration (eg parental vs local capsaicine) and sponsors should be able to justify, if a complete data set cannot be provided. Auxiliary products would include both non-IMP (rescue, background, challenge agents) as well as ancillary materials, such as infusion/saline solutions, etc. Please add specifically PET tracers used as a diagnostic agents and other diagnostics to the list of auxiliary medicinal products.
2.4. Insurance/indemnisation (p12)	We question how and who would define the "low-risk trials"? If indemnisation by Member States is only optional, there is a risk that Member States will not offer such insurance mechanism. How would compensation in those cases be ensured?
2.5. Single sponsor (p13)	We have no preference
2.6. Emergency clinical trials (p14)	No comment, we agree with the proposal.
3. Ensuring compliance with good clinical practices in clinical trials Performed in third	We agree with the appraisal. As it relates to clinical trial registration and results posting, we also support this proposal and would urge consistency with existing registration and results posting requirements that already are legislated in other ICH regions ie. US and the clintrials.gov. Mandatory inclusion of trials conducted in third countries into the

countries (p15)	EudraCT database would present an additional complexity and administrative burden requiring additional resources without additional public health benefits. The European Union should rather work collaboratively with other regions to co-ordinate the transparency of Clinical Trials without unnecessary duplication of registration or differing requirements. The Joint Industry position on the disclosure of Clinical Trial Information via Clinical Trial Registries and Databases[1] and the Joint position on the Publication of Clinical Trial Results in the Scientific Literature[2] discuss this topic and outline the principles of trial registration and result publication on a global basis. IFPMA has also established a clinical trials portal since 2005[3] which allows public access to clinical trial information from companies as well as clinicaltrials.gov. In addition, the WHO operates an International Clinical Trials Registry Platform to ensure that a complete view of research is accessible to all those involved in health care decision making[4]. In this respect, we strongly discourage the EU to require an additional mandatory registration of third country trials within EudraCT.

[1] http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/EN/November_10_2009_Updated_Joint_Position_on_the_Disclosure_of_Clinical_Trial_Information_via_Clinical_Trial_Registries_and_Databases.pdf

[2] http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/20100610_Joint_Position_Publication_10Jun2010.pdf

[3] http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm

[4] http://www.who.int/ictrp/en/

4. Figures and data (p16)	Clinical trials are the most expensive part of R&D.[5] As they are lengthy and costly, clinical trials constitute a very important component of the drug development process – approximately two-third (i.e., c. USD 590m) of average cost of molecule route to market is allocated to clinical trials.[6] Costs of clinical trials seem to have risen by one third between 2005 and 2007 due to increasing regulatory and other requirements.[7] Hearn et al. conclude from interviews with Directors and senior staff in 8 Clinical Trials Units (CTUs) in the UK "[…] that the EUCTD has resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials."[8] **Question: We would like to have VHP data for the good understanding of EU Agency collaboration**

[5] EFPIA (2010), The Pharmaceutical Industry in Figures, www.efpia.org

[6] PriceWaterhouseCoopers (2010), Clinical Trials in Poland. Key Challenges

[7] See Rawlins M (2008), De testimonio: on the evidence for decisions about the use of therapeutic interventions; in: Lancet 372:2152-61, p. 2156; Collier R (2009), Rapidly rising clinical trial costs worry researchers; in: CMAJ 180(3):277-278

[8] Hearn J, Sullivan R (2007), The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK; European Journal of Cancer 43:8-13, p. 8