Response to: Concept Paper of February 9th, 2011 submitted for public consultation by the European Commission on the REVISION OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

Submitted May 11, 2011 by the ITALIAN SOCIETY of PHARMACOLOGY – Section of CLINICAL PHARMACOLOGY

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*The **Italian Society of Pharmacology** (SIF) was founded in 1939. In 1996 it was recognised as a non-profit scientific association by the Ministry of the University, Scientific and Technological Research. It is a member of IUPHAR and EPHAR (Federation of the European Pharmacological Societies).*
The present membership of SIF consists of 1169 ordinary members, 12 honorary members and 20 supporting members.
The Society has a permanent office in Milan and is managed by a President, a President elect and a Steering Committee of 8 members. The Society includes a Section of Clinical Pharmacology which is managed by a Co-ordinator and a Steering Committee reporting to the President.
SIF is an active and lively society, which has gradually changed from a typical learned society devoted mostly to the exchange of scientific information among its members to a kind of professional society, which, without severing the scientific roots which represent its "raison d'être", aims to promote pharmacology in Italy by fostering pharmacological education within the University, the National Health System and the general public, by supporting young pharmacologists with travel fellowships and grants and helping them to find jobs, and by collaborating with public authorities and private organisations in disseminating expert opinions on drug efficacy and side effects.
Over the past 15 years, several pharmacologists associated to SIF have been appointed members in ethics committees operating in Italy according to the Ministerial Decrees regulating clinical trial approval in Italy.

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RESPONSES

Consultation item no. 1: Do you agree with this appraisal? Please comment.

Item no. 1: YES, but this would only decrease the administrative burden and insufficiently address the problem. The CTA evaluation could be somewhat accelerated in the EU, but the separate assessment will end up with different queries and results.

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

Item no. 2: YES, if the centralized procedure is followed by separate assessments, the process of CTA evaluation will not be significantly improved.

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

Item no. 3: the appraisal is very realistic. Centralized assessment will certainly be expensive in terms of resources needed and unattractive not only for academic researchers, but also for industry. The differences in ethical issues among the different EU members could determine longer evaluation procedures.

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

Item no. 4: Yes, the list appears to be complete; perhaps more details are needed under "trial design" and number of subjects to be enrolled.

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

Item no. 5: Yes, we fully agree.

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

Item no. 6: the first approach is preferable, because any judgement that there is a "serious risk to public health or safety of the participant" should not be mitigated by the 2nd or 3rd approach.

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

Item no. 7: the 2nd approach, because this is the type of trial for which there is a valid rationale for CAP. For its nature, CAP should be considered a harmonized assessment procedure among different EU members, aimed at evaluating a study protocol that should ensure coordination among member states in terms of planning, conducting the research and harvesting data.

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

Item no. 8: the pre-assessment procedure could be workable in practice, but an efficient selection of studies is required. We suggest assessing a random sample of 100 RCTs to verify applicability of the criteria and percentage of type-A trials.

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

Item no. 9: YES, the aim of a harmonized procedure for CAP should reflect the need to include the highest number of studies within the boundaries of the Clinical Trials Directive. On the other hand, more efforts are needed to make the definition of "non-interventional trials" less open to interpretation, with specific regard to the most common methodologies used for observational studies, which should be encouraged.

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

Item no. 10: YES, the Clinical Trials Directive should consider also academic / non-commercial sponsors. If the general aim of the present public consultation is to draw and plan a directive that could apply to multinational studies (whatever the sponsor, the drug, the enrolled subjects, etc), then the basic criteria should be very general, encompassing both commercial and academic sponsors.

Consultation item no. 11: Do you agree with this appraisal? Please comment.

Item no. 11: YES, especially for the third aspect. Please note that in Italy a decree is already in force on "detailed guidance on the request to the competent authorities and to the Ethics Committee for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial" (Ministerial Decree 21st December 2007).

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

Item no. 12: No, we do not have further suggestions.

Consultation item no. 13: Do you agree with this appraisal? Please comment.
Item no. 13: Yes, the appraisal is justified and we agree.

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

Item no. 14: the removal of insurance for low-risk studies should not be pursued. Even if the risk is low, subject should be protected. The second option could be a more reasonable approach and seems preferable especially for non-profit studies. A third option could be represented by grading the risk: this classification could help in solving the problem of defining a risk profile for the study, but this would probably require long preliminary work and not be feasible because of different perceptions of risk. We found it useful to consider the paper by Rid et al. on *"Evaluating the Risks of Clinical Reasearch"* (JAMA 2010; 304: 1472-1479), which provides a framework to minimise the influence of cognitive biases on the evaluation of research risks.

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

Item no. 15: YES. Option 1 is preferable.

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

Item no. 16: YES. Emergency clinical trials represent a critical area of research. This appraisal could be a first tentative step towards regulation of this type of clinical trials. From an ethical point of view, only when informed consent has been signed the patient may be enrolled, but in emergency this is not always possible (for example, it is difficult to enroll a sufficient number of patients during the first hours of their hospitalization in ICU). Furthermore, the situation *"The trial subject has not previously expressed objections known to the investigator"* should probably be reconsidered, because a procedure enrolling simply on the basis of the lack of patient's will seems hardly acceptable.

Consultation item no. 17: Do you agree with this appraisal? Please comment.

Item no. 17: YES, the appraisal is correct. This is a very important aspect. We have no further comments.

Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

Item no. 18: No, we have no further comments.