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**RESPONSE TO THE EUROPEAN COMMISSION CONSULTATION ON THE
ASSESSMENT OF THE FUNCTIONING OF THE CLINICAL TRIALS DIRECTIVE
2001/20/EC**

The Faculty of Pharmaceutical Medicine (FPM) is pleased to have the opportunity to respond to the European Commission Consultation on the Assessment of the functioning of the Clinical Trials Directive (CTD) 2001/20/EC. The FPMs Mission Statement is to advance the science and practice of Pharmaceutical Medicine for the benefit of the public. The Faculty is a professional membership organisation with approximately 1400 members who are practising or retired pharmaceutical physicians or those with an interest in the speciality. About 35% of members are based outside the UK.

The effect of the CTD has been mixed, good developments include the speeding up of ethical review but adverse developments include increased bureaucracy in getting clinical trials started and a failure to achieve good harmonisation across Member States. Western Europe and particularly the UK have traditionally been major sites for clinical research and yet Table 3 in the consultation document shows that after an initial increase in participants in trials, there was a 20% reduction in 2008 to a total below that of 2005 and the first three quarters of 2009 suggest a further decline. The FPM believes this is a serious situation in that with more potential participants available in Europe than there were in 2004/5, the number of planned participants is falling. With the pharmaceutical industry being global and being responsible for about two thirds of trials covered by the CTD, these figures demonstrate that Europe is losing its competitiveness particularly to Russia, India, China and parts of South America. There is no doubt that the CTD and its interpretation at National level is partly responsible for this decline. Furthermore, it is well accepted that patients in clinical trials do at least as well if not better than patients being treated for the disease but not in trials, and they have the potential to receive new innovative medicines as part of the trial. This decline in European participation thus has an adverse effect on the overall health of the people of Europe.

One of the primary purposes of the CTD was to ensure the simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost efficient clinical research. There has been harmonisation of maximum timelines for regulatory and ethical review but the excellent work done by the European Forum for Good Clinical Practice (EFGCP) in their recurrent survey of ethics committees in all Member states demonstrates the diversity of systems that currently operate. For sponsors doing multi-national trials in Europe this has become a major bureaucratic issue and persuades them to open sites outside Europe. Para 3.2 of the consultation paper reports one of the outcomes of the excellent ICREL Report indicating a doubling of staff needs within pharmaceutical companies for administrative work in submitting a Clinical Trial Authorisation (CTA). The FPM believes that this situation is not sustainable and will lead to continuing decline in clinical research in Europe.

There is no doubt that the varied interpretation of the CTD in Member State legislation has led to major differences between them and particularly in the UK, where waiting times to begin research have increased due to the need for approval of a clinical trial at local level. Although systems are being developed to improve the situation, it will probably not lead to an increase in trials but only a slowing in the decline

Consultation Item No.3

The FPM confirms that this is a valid description of the situation. We know of a recent example in which a protocol was accepted by a number of Member States (MS) but two requested changes to the protocol after the study had started in others. This situation leads to inconsistent recruitment due to different MSs starting at different times and inconsistent versions of the protocol being used across different MSs potentially jeopardising the validity of the data produced.

Consultation Item No.4

The FPM welcomes the efforts made by the National Competent Authorities in cooperating and jointly assessing requests for Clinical Trial Authorisations (CTAs) under the Voluntary Harmonised Procedure (VHP). However we feel that the time is now right for legislation to be introduced to ensure that all clinical trials involving more than one Member State should only be assessed by a lead Competent Authority (CA) chosen by the sponsor. Of course, the trial must have at least one site in that chosen CA.

Consultation Item No.5

The FPM prefers the option laid out under para 3.4.3 for the assessment of a CTA by ethics committees. It is vital that there is legal clarity for the respective scope of assessment by the CA and the Ethics Committee (EC). Overlaps must be avoided and a good example of an overlap that needs to be addressed is the requirement to provide SUSARs to both the CA and the EC, a totally unnecessary duplication and actually potentially harmful to patients.

Consultation Item No.6

The three examples given in the Consultation Paper at paras 4.1.1-4.1.3 are very real ones. There is no doubt that the legislation and guidance needs to be tightened so that it is very clear what is a substantial amendment, and what is not an interventional clinical trial and that needs to be clear throughout Europe. As outlined under the answer to Item 5, the issue of sending SUSARs both to CAs and ECs needs to be reviewed urgently and we would suggest that they should only be sent to the CA.

Consultation Item No.8

The FPM believes there is a lot to be said for introducing a Regulation as this would lead to complete harmonisation. However there are perfectly reasonable differences of opinion at a National level on certain types of clinical trials e.g. stem cell trials and these would need to be highlighted by the National Ethics Committee. Our proposal would be a hybrid of a Regulation and a Directive i.e. where there should be complete unanimity throughout Europe on certain aspects of the legislation, then the Commission should produce a Regulation, but where national differences are important then those should be covered by a Directive. We believe that the majority of the legislation could be covered by a Regulation but ethical issues would be left to Member States via a

Directive. We believe that sponsors would rapidly adapt to the system and if it improved overall timelines to receive a CTA, then this could well make Europe more competitive.

Consultation Item No.13

The FPM is totally opposed to excluding “academic” trials from the Directive. This would lead to a two-tier system which would not be understood by participants. The Faculty of Pharmaceutical Medicine runs an annual GCP examination and has done for a number of years. The results demonstrate an average of 80% of people from industry pass but only 40-50% from academia and the NHS. The examination is based on the requirements of ICH GCP which has essentially been legalised by the CTD. This statistic alone shows why academic trials must continue to be covered by the CTD but in a much less bureaucratic way for it is the bureaucracy that has been deleterious to academic sponsors. Furthermore, varying national definitions of “academic” could lead to further variation of the regulation of CTs across Europe thus jeopardising attempts to improve harmonisation.

Consultation Item No.14

The FPM recognises that the legislation for the development of Better Medicines for Children is covered by a Regulation whereas currently the clinical trials to support that development in Europe are covered by a Directive (the CTD). If our response to Consultation Item No.8 was introduced this would certainly benefit the development of medicines for children in Europe and so we commend it to the Commission i.e. a new Regulation for most of the aspects of the Clinical Trial legislation but with ethical issues covered at a National level.

Another area where this proposal would be effective would be in clinical trials for medicines that will be classified as orphan drugs, many of which are used in children.

Consultation Item No.16

The FPM recommends that all new legislation relating to clinical trials should have the Declaration of Helsinki 2008 or the most up to date version as its base reference.

Consultation Item No.17

The FPM would not support the total publication of all cases of non-compliance with GCP following inspection as the adverse findings do not necessarily impact on patient safety. However critical findings affecting patient safety should be published but so should follow-up inspections indicating whether the adverse issues have been resolved.

The FPM believes that any study that has an EC site should have a named EC based physician as the lead in Europe for that study.

Consultation Item No.18

One further area that needs review is the definition of a Clinical Trial. Currently it is not entirely clear whether the term “interventional trial” includes studies that are exploratory and often preliminary in the course of translational evaluation of either a specific Investigational Medicinal Product (IMP) or the concept testing of methodologies in different disease states. There are two classic examples of these types of studies. Firstly, the use of naturally occurring molecules as agonists (or more rarely antagonists) to evaluate a novel potential inhibitor or antagonist. Secondly, the study in volunteers or patients using medicinal products within their marketing authorisation to

evaluate a test system that might be used in future to measure the effects of an IMP. In both these situations, no medicinal product outside the licence is being administered.

One solution to this problem would be to institute a separate class of clinical trial to be called Clinical (or Investigational) Methodology Trials. Criteria would need to be worked up to differentiate them from audit, classical Phase I studies and from Phase II and III trials. Competent Authority and Ethics Committee approval would still be required for these trials but the current confusion would be resolved.

8th January 2010