

**WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS  
DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE  
FUTURE**

*Only one written submission by organisation to be submitted to the EMEA by 14 September 2007!*

**Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.**

<b>Name of Organisation</b>	<b>Country</b>
SIOP Europe (Société Internationale d'Oncologie Pédiatrique – European branch)	International

Please submit by 14<sup>th</sup> September 2007 at the latest to **Kati Almasi** on [CTCONF@emea.europa.eu](mailto:CTCONF@emea.europa.eu).

Please use the format provided – add as many additional boxes as needed.

## Aspects of the Directive 2001/20/EC that work well

Comments	Suggestions
1) Setting out general rules for the functioning of clinical trials including certain quality standards, has probably improved the rigour with which academic non-commercial clinical trials are conducted.	1) Regulatory requirements should take account of the level of risk involved in a clinical trial and should recognise that those that involve only “old medicines” with a track record of safety and known side effect profile in a particular patient group are low risk and should require a much lower burden of regulatory oversight than clinical trials involving new drugs or new approaches.
2) The move to create centralised European databases of clinical trials and safety data is welcomed and will be a valuable resource for researchers in the future, once established.	2) Access to the information contained within these databases should be kept simple for the occasional user.
3) For the CTA file initial submission, it is good that the CTA file contents are the same for all countries (study protocol, investigator’s brochure, CTA form, EudraCT number). However, at the CTA file assessment stage, each national competent authority has its own assessment rules which mean that the CTA can be modified at each submission according to national requirements.	3) A means to improve harmonisation between competent authorities should be found to reduce this variability, or to allow a single ‘European’ CTA approval that is then endorsed by each participating national competent authority, without repeating the whole process.
4) Some countries do not require electronic reporting of SUSARs by non-commercial sponsors, which has been very helpful. However, not all countries allow this flexibility.	

## Aspect of the Directive 2001/20/EC that do not work well

Comments	Suggestions
<p>1) The bureaucratic workload of trial activation is much too high for rare diseases like many childhood cancers. For the rarer subtypes of childhood cancer such as childhood liver tumours, centres may see between 0-10 recruitable cases during the lifetime of a 5 year phase III trial and even less for a phase II trial. Accordingly, the regulatory burden of activating such a trial with non-commercial (academic) sponsorship is disproportionate to the expected patient recruitment.</p> <p>Specific examples:</p> <p>The SIOPEL consortium has run clinical trials in childhood liver tumours since the early 1990s which have led to dramatic improvements in survival rates. Prior to the EU CTD, the SIOPEL International Collaborative Group ran phase III trials in hepatoblastoma in over 50 centres across Europe. However, the majority of SIOPEL centres have failed to activate two new SIOPEL trials; SIOPEL 4 (phase II single arm trial of intensified treatment for inoperable hepatoblastoma) and SIOPEL 5 (phase II single arm trial for childhood hepato-cellular carcinoma). Most centres would see less than two cases per year of eligible patients for these trials and find the bureaucratic burden too heavy to activate the trial in their centres. However, the same approach to treatment is being used by the majority of SIOPEL centres but without formal trial entry, meaning that valuable clinical outcome data is being lost and preventing progress in these rare diseases with poor outcome.</p> <p>The Langerhan Cell Histiocytosis (LCH) consortium (LCH III) trial has had much slower recruitment than anticipated or seen in previous trials by this consortium following introduction of the EU CTD</p> <p>LCH Salvage 2005:- aimed to improve remission rate (and survival)</p>	<p>1) The EU CTD should be amended to dramatically simplify regulatory approval procedures for rare childhood diseases where individual tertiary treatment centres may see between zero and a few cases per year. The experience of the several European study groups who have succeeded in launching childhood cancer clinical trials across the EU should be taken into account.</p>

<p>from 25% to 50% (which is the experience in pilot studies). However, opening has been severely delayed in most countries due to the requirements of the EU CTD. In the view of the Chief Investigator, this will have resulted in the death of young children who would have otherwise survived.</p> <p>The Innovative Therapies for Children with Cancer (ITCC) consortium, who design and run multinational clinical trials of novel therapeutic approaches for childhood cancer, have experienced disharmony between the Ethics committee assessments due to cultural differences in ethical review and processes between countries, e.g.:</p> <p>Italy: doesn't implement totally the Directive by the fact that there is one ethics committee approval per hospital.</p> <p>UK: complex system of MREC (Multicentre Research Ethics Committee) submission, hospital ethics committee submission and ARSAC (Administration of Radioactive Substances Advisory Committee) submission if necessary. These multiple levels of submission lead to significant delay in activating each participating centre, even though there is theoretically a centralised submission process.</p> <p>Germany, NL : the obligation is on the academic sponsor to prove that their clinical study is a non profit trial, especially at the ethics committee submission stage.</p>	
<p>2) It is extremely difficult to find a sponsor for paediatric oncology clinical trials.</p> <p>The need for a single pan-European sponsor is interpreted differently by different national regulatory authorities and has caused severe delays to launch of new protocols by long-established European collaborative groups.</p> <p>Specific examples:</p> <p>Interfant 06, a randomised trial aiming to improve outcome and reduce toxicity in the very rare group of infants (aged less than 12 months) with acute leukaemia has been very slow to open across Europe, as many countries are still struggling with the procedures, in particular sponsorship. This trial is a collaboration between eleven established</p>	<p>2) The responsibilities of the international sponsor should be clearly defined and limited to those of coordination, as suggested in our previous letter to Dr Santos-Ivo, 18<sup>th</sup> Dec 2006:</p> <ul style="list-style-type: none"> <li>• Assuring that the appropriate organisational structure is put in place with national representatives, each of whom confirms that their centre/national group's participation complies with national laws and,</li> <li>• Responsibility for timely communications with all partners of relevant information required by regulatory authorities for safe conduct of the trial.</li> <li>• Also, consideration should be given to providing the necessary support, at a European and/or national level, to allow academic institutions or governmental research bodies to feel more comfortable</li> </ul>

<p>European groups yet 18 months after the launch of the trial, only six of the EU countries were able to formally open it.</p> <p>German institutions and the GPOH Liver Group, although willing to join the SIOPEL family of trials, are unable to do so because of the strictness of the German law dealing with sponsorship issues which appears to be extremely difficult to solve at a national level.</p> <p>Innovative Therapies for Children with Cancer (ITCC) consortium:</p> <p>Difficulties in finalising the co-ordinating sponsor – co-sponsor agreements which define the role and responsibilities between both parties has been a prolonged process because of specific requests (for modifications) from each co-sponsor.</p>	<p>with taking on the role of European sponsor for non-commercial, investigator-led clinical trials. This is a particular issue for trials involving children, where the perceived risk to the sponsor is felt to be greater than for adult trials by many institutions who are unfamiliar with research on children, thus making them reluctant to accept this role.</p>
<p>3) The requirement for the sponsor to provide free drug is problematic in those countries where treatment within a non-commercial clinical trial is not resourced within their national health care systems.</p>	<p>3) The obligation on the sponsor to ensure that clinical trial participants have access to free drug should be reviewed for academic-led trials without a commercial partner.</p>
<p>4) The variable approach between countries in the definition of what constitutes a clinical trial has led to large and absurd discrepancies in the bureaucracy and resources required to administer a standard arm treatment within a clinical trial.</p> <p>Specific example:</p> <p>The European paediatric soft tissue sarcoma group’s clinical trial for the treatment of localised rhabdomyosarcoma includes a single arm treatment recommendation that is considered ‘best practice’ or standard of care, for ~ 50% of patients enrolled in the current trial and for which there is long established safety and outcome data. Some countries demand that all patients registered with the trial are treated as clinical trial patients, with associated pharmacovigilance, whereas others have permitted separation of this group with reduced reporting requirements.</p>	<p>4) A means should be found to allow consistent application of ‘standard of care’ treatment guidelines with associated relevant clinical data collection without this being classified as a ‘clinical trial’. Guidance should be clear so that the approach is consistent between countries.</p>
<p>5) Liability insurance: there is tremendous national variation in the requirement for this and its cost.</p>	<p>5) There should be no absolute requirement for liability insurance for out of patent medicines used off-label in the paediatric setting, where such use is well established as part of standard practice. The requirement for liability insurance should take account not only of the risk of receiving the treatment but also the risk to the child’s life of not receiving potentially curative therapy.</p>

<p>6) The identity of the Competent Authority for academic trials depends on the country, e.g. in the experience of the ITCC consortium for paediatric trials of new drugs which have pre-existing marketing authorisations for adult use: in Italy, an academic institution appears to be able to take on the responsibilities of the competent authority for non-commercial trials when the IMP is already registered in the country. The hospital insurance then covers the potential risks due to the trial. In France, UK, NL, Germany, the national health authority assumes some or all of these duties.</p>	<p>6) Need to harmonise the definition of the Competent Authority.</p>
<p>7) Need for identified trial drug supply for off-patent medicines that are manufactured generically by different suppliers in different countries.</p>	<p>7) Where a medicine is off-patent, national regulatory authorities should not demand that the protocol has to specify the drug supplier.</p>
<p>8) The need for labelling of IMPs is variably interpreted by different national regulatory authorities and can be onerous.</p>	<p>8) See above.</p>
<p>9) The requirement for an IMP dossier by every national regulatory authority has led to unnecessary duplication of effort and slowing of the bureaucratic process to approve a trial.</p> <p>Specific example from the ITCC consortium: difficulties in obtaining the investigator's brochure from manufacturers for academic studies and logistic issues in the case where different manufacturer's subsidiaries are involved in the product distribution, have led to long delays in putting together the IMP dossiers.</p> <p>Germany / UK : the competent authority (Bpharm and MHRA) ask for the IMP to be completely similar to the authorised product, which means that it is impossible to provide Germany and the UK with a commercial product registered/packaged in France.</p>	<p>9) A single European submission of an IMP dossier should be sufficient for a drug to be used in a clinical trial run in several Member States and to define what is expected for adverse event reporting.</p> <p>Again, this emphasises the problems caused for paediatric trials of drugs that are called 'IMPs' but which already have a marketing authorisation for adult use and which can be supplied from different routine sources in different countries. Such drugs should be allowed to be supplied from different sources in accordance with each institution's normal suppliers.</p>
<p>10) Pharmacovigilance – there are large differences in national interpretations concerning reporting of SUSARs. This is a particular problem in Germany where expedited reporting is required even for SUSARs occurring in other trials that use the same product if the sponsor is in common and not the holder of the marketing authorisation.</p>	<p>10) National variations in requirements for expedited reporting of SUSARs should be reviewed and harmonised to the minimum standard that is agreed to be compatible with patient safety.</p>
<p>11) There is the unknown negative effect that the EU CTD has had on trials that have never been launched, since academic consortia have been deterred by the cost and erosion of personal time involved in launching a new trial under the current bureaucracy. Some very clever ideas may</p>	

have been lost as a result and are most likely to affect patient groups with the least common disorders.

## What can be remedied within the present legal framework (by modification of guidelines or clarifications)?

Comments	Suggestions
<p>1) The key issue is the need for and unlimited responsibilities of the international trial sponsor.</p>	<p>1a) Creation of a pan-European sponsoring body for paediatric non-commercial trials or trials of very rare diseases in other age groups.</p> <p>1b) Have very clearly defined and limited responsibilities of the international sponsor, confined to coordination and communication duties.</p> <p>1c) The variation in national interpretations of the need for a single (academic) sponsor per trial and the varying attitudes to the status of national co-sponsors for multi-national trials must be harmonised, to allow certain countries (e.g. Germany) to join such trials.</p>
<p>2) Definition of IMPs</p> <p>There are national variations in whether health insurance systems cover the cost of IMPs. This has led to the ludicrous situation where a child's treatment can be covered by health insurance if they are not enrolled in a clinical trial, yet the same treatment may require funding from the (limited) clinical trial resources if given within the context of a trial.</p>	<p>2a) Off-patent drugs should not be defined as IMPs simply because they are the subject of a randomised comparison.</p> <p>2b) 'Old' drugs that would be classed as IMPs purely because their marketing authorisation does not include paediatric use but which have a long track record of safe/manageable and effective use in children, should be included under the definition of non-IMPs.</p> <p>2c) There should be some harmonisation of national attitudes to funding IMPs within national healthcare systems for non-commercial trials, especially when they involve drugs with existing marketing authorisations in adults but which have not yet been fully evaluated in children.</p>
<p>3) Labelling of IMPs</p>	<p>3) The requirement for labelling of IMPs should be modified to allow any reputable, commercially available supply of a drug that is already marketed for adult use, to be used within a paediatric clinical trial across several countries.</p>
<p>4) Definition of a clinical trial and need for pharmacovigilance when the trial question is optimisation of long established use of drugs used off-label in the</p>	<p>4) Such trials should have greatly reduced regulatory requirements.</p>

paediatric age group.	
5) Pharmacovigilance: Multiple declaration of the SUSAR's to the national health authorities/competent authorities causes unnecessary duplication of effort and paperwork.	5) Could be replaced by a unique declaration to Eudravigilance.
6) Although there is already in place in the EU CTD the ideal of harmonisation of ethical standards and processes, there remains considerable disharmony in their implementation between countries.	6) We hope that this timely review of problems experienced by the academic, non-commercial clinical trial sector, stimulates a review of adherence to the suggested pan-European guidelines for the operation of ethical review processes for clinical research and leads to a simplification of procedures in all countries.

### What should a new legal framework look like?

Comments	Suggestions
<p>1) A means should be found to simplify the regulatory approval and registration processes for paediatric non-commercial trials in order to sustain the necessary level of clinical research for progress in therapy of childhood cancers.</p> <p>Although a single pan-European ethical approval body for international trials is viewed as desirable by some groups, this is not felt to be either practical or desirable by others. However, all would support a single ethical standard for clinical trials in children.</p>	<p>1) There should be only one international (European) necessity to register the trial without any further need for national registrations, for uncommon conditions.</p> <p>There should be a review of adherence to the suggested pan-European guidelines for the operation of ethical review processes for clinical research with the aim of simplifying procedures in all countries. In particular, it should be investigated whether countries that appear to have complied with the single ethical opinion for clinical trials have simply replaced the institutional control with another layer of bureaucracy, variably labelled 'Research &amp; Development' approval. Furthermore, there should be no fees charged for non-commercial trials.</p>
<p>2) Rules of sponsorship should be modified and relaxed for paediatric non-commercial international trials since currently they create a significant obstacle for several countries and centres to join. This should be applied especially to rare diseases, where the current administrative burden is so large and disproportionate to expected patient numbers that many centres prefer not to participate in such trials, in order to register one or two</p>	<p>2) A pan-Europe body could be created which will take a role of an overall international sponsor for various paediatric trials. Otherwise legislation could be modified and in non-commercial trials the sponsor could bear only scientific and coordinating responsibility, while medical liability should be delegated to the national level or even the level of individual treatment institutions. This would encourage international and national research or</p>

patients per year.	academic institutions to accept sponsor's role.
3) Additionally national public research or clinical institutions are reluctant to take the international sponsorship role since it is associated with significant liability and legal responsibility.	3) As stated above the legislation could be modified and in non-commercial trials the sponsor could bear only scientific and coordinating responsibility (including SAEs and SUSARs management), while medical liability should be delegated to the national level or even the level of individual treatment institutions.
4)	4)
5)	5)
...	...