



12th October 2007

By email: CTCONF@emea.europa.eu

Arielle North and Fergus Sweeney
EMA, 7 Westferry Circus
Canary Wharf, London, E14 4HB

Dear Dr North and Dr Sweeney,

Thank you for giving us the opportunity to attend the joint meeting between Regulators, clinical trialists and the European Commission held on October 3rd, 2007 at the EMA, to represent the point of view of academic clinical researchers in the field of childhood cancer working in Europe.

We found the presentations and discussion stimulating but were concerned at the apparent divide between the views of the Regulators and those of the clinical trial groups. Clearly, there is a very marked difference in the perception of where the block to clinical research lies. We were very concerned to see that the presentations from the representatives of the Clinical Trials Facilitation Group thought that the EU Clinical Trials Directive was basically sound and that only some "fine-tuning" was necessary. This is very far away from the view held by the academic clinical trials community, who have struggled to find the resources (man-hours and money) to meet the exacting standards now required by the Regulators. These were designed to meet the needs of early phase clinical trials and our experience is that they have not improved patient safety in phase III trials. Indeed, the diversion of scarce resources to comply with the EU CTD has, in our view, compromised access to clinical trials, which are viewed as best standard of care for children with cancer. This has been a particular problem in paediatrics, where many drugs are used "off-label" since their manufacturers have never been required to address paediatric needs in their marketing authorisations. We appreciate that this situation is set to improve for the better for children with the Paediatric Regulation. However, the majority of clinical trials in childhood cancer, and indeed in paediatrics in general, will continue to test optimisation of therapy using existing products, many of which are out of patent. These are mainly used outside of their licensed indication, due almost exclusively to lack of testing in the paediatric age group.

Most of the issues we raised in our written submission on behalf of professionals treating children with cancer in Europe were addressed during the meeting on October 3rd. However, we would like to reemphasise two areas that cause us particular concern across several European countries and which we hope can be resolved by this fresh look at the European Clinical Trials Directive.

One issue that was not discussed at the meeting on October 3rd and which is having a major and disproportionately negative impact on clinical trials in children, is the definition of IMPs. The majority of phase III trials in childhood cancer compare two long established therapies, each of which would be considered "standard of care" by different national groups or introduce a new risk stratification. Alternative designs are to intensify a standard backbone or sometimes to test the removal of a drug with known long-term side effects in the growing child (e.g. doxorubicin). If one takes the strictest definition of IMP, when applied to a product with a marketing authorisation, namely "when used for an unauthorised indication", then the majority of paediatric use of the current armamentarium of anticancer products falls into the "off-label" category. Since the majority of these drugs are already out of patent, there is no commercial interest in developing these products to include a paediatric indication in their marketing authorisation. Therefore, clinical trials in children which use these drugs have a disproportionate bureaucratic burden imposed upon them by the need to treat these drugs as IMPs. We did submit detailed comments on this point to the European Commission's Consultation on

Professor Kathy Pritchard-Jones, PhD, FRCPE, FRCPC
President of SIOPE Europe and Chairman of the SIOPE Clinical Trials Committee

Tel: +44 (0) 208 661 3498
Fax: +44 (0) 208 661 3617
E-mail: Kathy.Pritchard-Jones@icr.ac.uk

SIOPE Europe Secretariat: Jocelyne.Wang@ecco-org.eu
Avenue E. Mounier, 83 - B-1200 Brussels - Belgium

IMPs in Non-commercial Trials, in September 2006. We were therefore disappointed to see that the recent guidance on IMPs, issued May 2007, made no mention of any special consideration for off-label use of drugs in children, when they have a long established safety and efficacy profile.

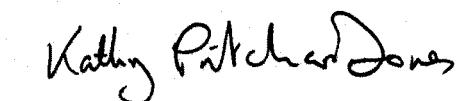
We urge the Commissioners to readdress this important question in order to exempt the routine definition of any off-label use of a drug in children as an IMP within a clinical trial. Even with the reduced labelling requirements for marketed products described in Annexe 13 of the European Commission Guidelines on Good Manufacturing Practice, this places an unworkable administrative burden on already overstretched pharmacy staff. In some circumstances, these labelling requirements can negatively impact on recruitment to clinical trials, since it is likely that children would have to return to their main treatment centre for dispensing of all of the drugs they receive in the trial, whereas if they were a non-trial patient, they could easily receive the same medication via their local hospital, with considerable benefits for the quality of life of the entire family, such as increased school attendance, less loss of parental work time and earnings etc.

We appreciate that the definition of IMPs and how strictly the guidance on labelling requirements etc is followed shows different national variations. Some countries are accepting that drugs with a long established safety and efficacy profile in children may not be defined as IMPs even though they are being used outside of their marketing authorisation. Clearly, it would be a benefit to children if there could be a harmonised approach to defining what should and should not be considered an IMP in relation to its use in childhood cancer, or indeed any paediatric disease. We would urge the Commission to facilitate a means whereby each of the currently used anticancer drugs without a licensed paediatric indication can be evaluated for their safety and efficacy profile to produce a common dossier that all clinical trialists using these agents could refer to, in order to exclude their medicine being defined as an IMP. However, although the academic paediatric community has the expertise, it does not have the resources and administrative support to produce the required documentation in isolation.

The final point which we wish to reemphasise but which was well discussed in the meeting, is the issue of trial sponsorship. We were disappointed to see that the representatives of the Regulators did not appreciate how great an obstacle this is to launching clinical trials. Indeed, as exemplified in our written submission, several important clinical trials in rare childhood cancers are failing to be activated in several centres or countries, due to the disproportionate bureaucratic workload to recruit just a few patients. In the meantime, the standard arms of these trials are being used as best practice (which indeed they are) but valuable clinical patient data is being lost to the trial. In our view, it is unreasonable to expect universities to accept the role of pan-European sponsor with all of the responsibilities as currently defined, as they have no aegis or understanding over healthcare systems in countries other than their own. This is a very important issue which must be solved in order to facilitate multinational non-commercial trials in Europe. In our written submission, we did make a suggestion that the roles and responsibilities of the pan-European sponsor could be limited to those of communication and coordination. However, this requires well-written contracts between the national co-sponsor and the overall sponsor. Currently, each trial group is drawing up these contracts from scratch with all of the expense of involving international lawyers etc. Again, it would seem sensible to have a harmonised approach and a single source of the necessary information and template contracts for academic trials to use.

Thank you once again for giving us this opportunity to provide you with the experience of the clinical trialist working in the field of childhood cancer across Europe. We trust you find our comments valuable and that they can be incorporated into a revision of the Directive.

Yours sincerely



Kathy Pritchard-Jones
President, SIOP Europe and
Chairman of the SIOP Europe Clinical Trials Committee