Implementing the EU Directive

Update from the Netherlands

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Over the last few months, not much concrete news has emerged regarding the implementation into the Dutch law of EU Directive 2001/20/EC. To break this silence, on October 5th 2005, the Netherlands Association of Pharmaceutical Physicians organised a meeting together with the Central Committee on Research Involving Human Subjects (CCMO) and Ministry of Health, Welfare and Sports (VWS). The meeting, entitled 'EU CTD between the lines; its practical implication', was attended by about 300 participants, representing all stakeholders in Dutch clinical research. The meeting also launched an Instruction Manual on how to conduct clinical research under the new legislation, which can be ordered or downloaded from the CCMO website.

The meeting was opened and chaired by Herman Pieterse from Profess Medical Consultancy BV, who had been instrumental in the creation of the Instruction Manual. The EU Directive was to be implemented in a revision of the existing Medical Research on Humans Act (WMO). Herman said that, since progress was suspended by the Upper House of Parliament in December 2004, the Ministry of Health had worked to create a 'novelle' or amending Act to the proposed WMO. This novelle first needed support from the Lower House before being passed to the Upper House (the novelle was accepted by the Lower House on October 27th, and the WMO, as amended by the novella, was accepted by the Upper House on November 22nd*). Another law, the Medicine Law, also required amendment, and this was in its final stage at the time of the meeting. The purpose of this meeting was to share the latest news and, further, to offer practical advice to everyone in the field on how to work once the new law comes into effect.

Changed roles

Ms M Elenbaas of the VWS introduced the changes made by the novelle to the responsibilities of each committee/body. For nearly all research projects (except for those involving gene therapy, xenotransplantation etc.), an accredited METC (independent ethics committee) will review the application. This review may take up to 60 calendar days, and must include the investigational medicinal product dossier (IMPD). Therefore, each accredited METC must have at least one accredited clinical pharmacologist plus one hospital pharmacist (however, one person can fulfil both roles). A secondary compulsory review will be performed by the CCMO (Central Committee on Research involving Human Subjects, acting as the Competent Authority) and this may take up to 14 days. The sponsor may decide that this review takes place in parallel. CCMO's review will be largely limited to searching the EudraVigilance databases for the existence of any grounds for non-acceptance.

Any pharmacies that will play a role in the manufacture of investigational medicinal product (IMP) will need to be licensed to assure operating to EU-GMP (see www.farmatec.nl). Manufacture is defined as anything beyond the regular diluting of a lyophilised product with saline for injection or the labelling of a vial according to a randomisation list. Another license is required to import IMP from any non-EU country. There will be no longer be any requirement to inform the Dutch Inspectorate of Health (IGZ) of any planned import of unregistered IMP. Furthermore, the Qualified Person, who acts on behalf of the manufacturer's license holder, will have important roles relating to the quality aspects of the batches produced and released. These IMP-related items will be covered by changes to the text of the Medicine Law (most notably via changes to the enacting Decree BBA), which is anticipated to be in effect by mid-2006. The Medicines Evaluation Board (CBG) will be responsible for routing all necessary information into the new EUDRA databases and IGZ will ensure that all parties will comply with the relevant regulations.

Further professionalisation of ECs

Moving on to changes in the ethics review community, Dr J Oomen of the Dutch Society of METCs reported that, following the implementation of the first edition of the WMO (2001), the number of accredited METCs has dropped from 81 to 34. Dr Oomen presented the results of a telephone survey he had conducted with the 17 largest METCs (collectively responsible for 91% of all application reviews in 2004). In 2004, all 17 were already composed in compliance with the proposed WMO (as described above) and reported a tremendous increase in their professionalism. Only on three occasions had an METC experienced doubts over whether their internal expertise was sufficient to review an IMPD.

Working groups on several topics had been established to advise on the sharing of SOPs and to provide input for a new internet portal (see below). The joint development of a template protocol and a template application dossier will further help streamline the application process, most notably for the academic researcher. After the implementation of the novelle, the application dossier must contain documentation of the sponsor's liability insurance, sample IMP labels (in Dutch), the CV of each Principal Investigator of each Dutch site, plus (where already available) photocopies of any opinions on the protocol from foreign Competent Authorities (CAs) or Ethics Committees (ECs).

The meeting continued with a look at site-specific assessments. Dr P Salden from Nefarma observed that the current feasibility check performed by the Hospital Board of each participating Dutch site is taking too long. Based on preliminary results of 387 studies submitted in 2004, the average time to obtain this local approval was 75 days compared to the target time of 30 days stated in the CCMO decree of May 2004. As the local feasibility check will remain applicable under the new WMO, Dr Salden called for further streamlining at both the sponsor's and the hospital board offices.

Internet portal & reporting of SUSARs

Dr M Kenter from the CCMO updated delegates on the internet portal, called 'ToetsingOnline' (Review Online). This portal will be in effect from the moment of publication of the new WMO and will support online applications, downloading of EudraCT information into the electronic application form, direct links to www.clinicaltrials.gov (if permitted by sponsor) and to the EudraVigilance database (with automated notification to all parties by email), plus online SUSAR reporting (eSUSAR). Most importantly, the portal will allow sponsors, agents acting on sponsor's behalf, investigators, METC members, CCMO and CA staff, and (to a very limited extent) the general public, to view the timelines and follow the progress of the trial application, tailored to their respective role/ authorisation level. Therefore, the portal is expected to decrease bureaucracy, and make timelines more transparent and the process easier to understand.

The forthcoming requirements for SUSAR reporting were presented by Dr W van der Giesen from the CBG. Under the new legislation, all SUSARs must be reported electronically by the sponsor to the EudraVigilance database, using ICH reporting standard E2B/M. Next, the sponsor reports the SUSAR to the CCMO (who relays it to the relevant METC) by using the eSUSAR module in the internet portal. This module supports direct downloading from the E2B electronic report and will have two additional questions (one on causality and one on foreseeable consequences on the conduct of the trial). The SUSAR report must still be forwarded to the relevant METC. Sponsors will also be obliged to use the portal to report follow-up to a SUSAR, plus for the regular line listings and yearly safety reports. Exceptions are in place for Sponsors who are unable to report via E2B/M (yet), and for academic researchers. For these groups, the eSUSAR form can be used to report to the portal and LAREB will be responsible for reporting the event to EudraVigilance database. LAREB is the government centre for knowledge about adverse drug reactions in The Netherlands, normally involved in dealing with reactions to registered drugs.

Finally, Dr van der Giesen stated that he saw an increased role for independent Data Safety Monitoring Boards in terms of dealing with the (unblinded) SUSARs internally, and emphasised the need for clear definitions of when a serious event will be considered drug- or disease-related.

After the final presentation, a panel discussion was held. One topic predominantly was being discussed: the local feasibility statement to be issued by a hospital Board of Directors (usually the actual task of producing this statement is delegated to the hospital-based METC). After implementation of the CTD this item will remain, suggesting that parties should plan some extra time for this when planning multi-centre trials. The meeting was officially closed by Prof A Cohen, chair of the Working Party for CTD implementation, who formally presented the first copy of the new Instruction Manual to Mr H Hurts, director Drugs and Medical Technology of VWS.

Final steps to implementation

The next step is the publication of a few supplementary guidelines. It is anticipated the revised WMO will be in effect in the spring of 2006. Until then, the current guidance for trial applications must still be followed. As such, no EudraCT number or decision from the Competent Authorities is required, the only condition being METC approval.

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Useful websites

- Central Committee on Research Involving Human Subjects (CCMO), www.ccmo.nl. Copies of the Instruction Manual (in Dutch or English) can be downloaded or a printed copy ordered via this website.
- Ministry of Health, Welfare and Sports (VWS), www.minvws.nl
- Dutch Inspectorate of Health (IGZ), www.igz.nl
- Medicines Evaluation Board (CBG), www.cbg-meb.nl
- Nefarma, www.nefarma.nl
- LAREB, www.lareb.nl