UK launches CRO model Clinical Trial Agreement

The UK Department of Health has introduced a new Contract Research Organisation model Clinical Trial Agreement (CRO mCTA). It replaces the many different contracts that CROs have had to negotiate with individual hospital trusts. The Association of the British Pharmaceutical Industry welcomed the move, saying, “Many commercially-sponsored clinical trials involve a Contract Research Organisation and this agreement will enable those trials to start faster by reducing the bureaucracy around the clinical trial process.” The new contract is a tripartite agreement between the pharmaceutical company sponsoring the trial, the CRO managing it and the NHS Trust where the trial takes place. It will complement the bipartite agreement model used by pharmaceutical companies and NHS Trusts.

CEO to be held accountable for GxP assessment

The UK’s Medicines and Healthcare products Regulatory Agency proposes to move to risk-based inspections. Companies will be required to submit self-assessments on how they will comply with relevant good practices (GxPs) and CEOs will be held accountable. Read more in ‘What’s New’ at <canarybooks.com>.

Procedures for the EMEA inspection of sponsors and CROs

The European Medicines Agency (EMEA) has published Procedure Number INS/GCP/3, detailing the procedures it follows when conducting GCP inspections. Annex IV, which lists the main trial aspects that are verified at the sponsor site or the contract research organisation (CRO) performing sponsor’s trial-related duties, is reviewed on page 2.

Device sponsor failed to give inspection access to FDA

The sponsor of a trial involving a significant-risk medical device, who failed to allow the FDA access to its premises for inspection, has been found to have violated Investigational Device Exemption regulations. A recent FDA warning letter revealed that on three occasions in 2006 the FDA specifically asked the sponsor to provide accurate, complete and current information about the study. However, the sponsor failed to do this. Furthermore, FDA inspectors failed to gain access for inspection. Report on page 5.

UK’s Gene Therapy Advisory Committee releases annual report

The Gene Therapy Advisory Committee has published its latest annual report, summarising the activities it undertook in 2006. Further information on page 7.

The evolving FDA Critical Path Initiative

An interview with Janet Woodcock, Deputy Commissioner and Chief Medical Officer of the FDA, provides an insight into the progress of the FDA’s Critical Path Initiative. See page 4.

Is the FDA failing to oversee clinical studies?

In a report released at the end of September, the Inspector General of the US Department of Health and Human Services claimed that the FDA does little to ensure the safety of the millions of people who participate in clinical trials. More on page 6.

Electronic and paper versions available Visit: <www.canarybooks.com>
EMEA inspection of sponsors and CROs

The European Medicines Agency (EMEA) has released details of the main trial aspects that it verifies during GCP inspections of sponsors and contract research organisations (CROs).

In September 2007, the EMEA published information on the procedures it follows when conducting GCP inspections. Procedure Number INS/GCP/3 on Conducting GCP Inspections includes a number of annexes. Of these, Annex IV provides details of specific items that may be verified at the sponsor site or the CRO performing sponsor’s trial-related duties, as part of an inspection requested by the EMEA.

The actual selection of items to be verified will depend upon the scope of the inspection and will be established in the local inspection plan. In general, during the inspection an appropriate sample of data, documents and items from specific trials should be checked to confirm the functioning of the process described. However, the selection will vary depending on whether the inspection is a system inspection or a specific clinical trial inspection.

System inspection
A system inspection aims to evaluate the quality assurance (QA) and quality control (QC) systems established by the sponsor/CRO, in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The following items will be reviewed in a sponsor/CRO system inspection.

Organisation and personnel. Inspectors will evaluate whether the sponsor/CRO has a well-established organisation for clinical research activities and has a sufficient number of properly qualified and trained personnel for each area. The review will therefore cover:

- organisational charts that identify the key personnel in each area
- the independence of the QA unit
- the job description, qualifications and training of individuals involved in the clinical trial process.

Facilities and equipment. The aim is to identify and evaluate the facilities used for archiving or investigational medicinal product (IMP) storage, as well as the equipment used. Special attention should be paid to computer systems in order to evaluate their validation status, and their adequacy for the requirements of the trial(s) being inspected.

Sponsor/CRO operating procedures (SOPs). SOPs will be reviewed in order to verify their compliance with GCP standards and applicable regulations. This will include:

- implementation, monitoring and termination of the clinical trial
- IMP and sample management
- safety and adverse event (AE) reporting
- data handling and the clinical trial report (CTR)
- documentation archiving
- sponsor audit and the QA system
- delegation of duties.

Specific clinical trial inspection
A specific clinical trial inspection aims to verify whether the trial has been conducted and data have been generated, documented and reported in compliance with the protocol, GCP principles and sponsor procedures. The procedures and requirements applicable at the time of the trial should be considered, and compared where relevant with those applying at the time of the inspection.

Specific clinical trial inspections can also be conducted to answer questions listed in the Committee for Medicinal Products for Human Use request for a GCP inspection. Aspects that will be checked include the following.

Implementation and termination of the clinical trial. Inspectors will determine whether all legal and administrative aspects of the clinical trial have been accomplished. Review will therefore cover:

- distribution of the sponsor’s duties or functions
- information/training given to investigators...
• investigator selection and agreements
• fulfilment of regulatory requirements
• submission and approval of amendments
• critical dates (e.g. ethics approval/opinion, regulatory authorisation, study initiation, patient enrolment period, closing of trial sites, termination).

**Monitoring.** Aspects to be checked will include:
• availability, content and compliance with the monitoring plan and SOPs
• frequency and extent of monitoring activities
• monitors’ qualifications
• monitoring visit reports and their review by the sponsor/CRO
• corrective actions induced by monitoring visits.

**IMP.** Inspectors will check documentation related to:
• manufacturing, packaging, labelling and QC
• supply, accountability, returns and destruction (IMP tracking system)
• randomisation, code breaking and blinding
• shipment and condition of shipped product on receipt and during storage.

**Safety and AE reporting.** This will include checks of notification, follow-up and reporting of adverse events requiring expedited reporting, and safety updates and their communication.

**Case report form (CRF) data verification.** A selected number of CRFs will be checked to verify:
• adherence to the protocol, data accuracy, completeness, legibility and timeliness
• CRF corrections
• correspondence of the dates of first patient in and last patient with the dates of study initiation and completion, as well as with IMP delivery.

**Data handling and CTR review.** The following will be checked:
• the data tracking system from CRF to database
• validation of computer systems
• data management and statistical analysis as established in the protocol
• CTR content and system for review and sign-off
• QC applied.

**Clinical trial documentation and archiving.** These checks will determine if all essential documents are available during the inspection.

**Audit.** The inspectors will determine whether the trial was audited, will check the qualifications of the auditors and will confirm that audit reports exist.

The evolving FDA Critical Path Initiative

In a recent interview with the American Society of Clinical Oncology (ASCO), Janet Woodcock – Deputy Commissioner and Chief Medical Officer of the FDA – provided an insight into the progress of the FDA’s Critical Path Initiative (CPI).

The interview with Janet Woodcock and Samir Khleif (Special Assistant to the FDA Commissioner) was published in the October 2007 edition of ASCO News & Forum and describes how improved research methodology is supporting the FDA’s CPI.

The CPI was launched in March 2004, with the release of a report entitled ‘Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products’ (see <www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>). The initiative is the FDA’s endeavour to stimulate and facilitate a national effort towards modernising the scientific process through which a potential human drug, biological product or medical device is transformed from a discovery (or ‘proof of concept’) into a medical product. It also aims to identify and prioritise the most pressing medical product development problems, and the greatest opportunities for rapid improvement in public health benefits.

When the FDA launched the CPI, it aimed to bridge the gap between basic scientific research and the medical product development process. The interview highlighted that

- the drug development process and the high attrition rate for compounds entering testing are unpredictable in nature
- in reality, we still lack the tools needed to predict how well a treatment or diagnostic product is going to perform
- progress is being made at the molecular level and with tools from genomics, proteomics and imaging, but there is scope to improve the development process
- biomarkers, in areas such as oncology, have the potential to help clinicians to identify the type of tumour a patient has and whether it will respond to a particular therapy, based on factors such as prognosis, aggression, gene expression and the proteins on the surface of the tumour cells; unfortunately, gene expression profiling has been an industry buzzword for some time but has yet to reach routine clinical practice
- the CPI aims to put into place the regulatory process to enable sponsors to make submissions that can be discussed with the FDA in a comparatively informal way. The first gene expression assay in breast cancer has now been approved and more are expected.

In March 2006, the FDA’s Critical Path Opportunities List (see <www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf>) was released, describing the areas of greatest opportunity for improvement in the product development sciences. It included 76 concrete examples of how new scientific discoveries – in genomics, proteomics, imaging, bioinformatics, etc – could be applied during product development to improve the accuracy of the tests used to predict the safety and efficacy of investigational medical products. A number of these projects are now underway, including

- work with the Juvenile Diabetes Research Foundation on standards for an artificial pancreas
- a collaboration with Duke University on drug eluting stents
- safety biomarker research with the Critical Path Institute’s Predictive Safety Testing Consortium.

More information on the CPI is available at the dedicated FDA site <www.fda.gov/oc/initiatives/criticalpath/>.

Training in clinical research & GCP

Brookwood International Academy’s 2008 dates for their Basic (Part 1) and Applied (Part 2) courses leading to the Certificate in Clinical Research & GCP are now available at <www.brookwoodacademy.org>.
The FDA's Center for Biologics Evaluation and Research has issued a warning letter to the sponsor of a study involving a vascular closure system (VCS), a combination product subject to regulation under the Federal Food, Drug, and Cosmetic Act, including the IDE regulations (21 CFR Part 812). According to these regulations, compliance with all provisions is required as the product is a significant-risk device.

The warning letter begins by acknowledging that the sponsor correctly filed an IDE application for the device, but that in August 2005 it then submitted a Request for Designation stating that the product should be regulated as a Class III medical device. In March 2006, the FDA approved the IDE subject to certain conditions. However, instead of proceeding with the approved study, the sponsor initiated a study outside the IDE regulations, without informing the FDA. When the FDA learned of this study, the sponsor withdrew the IDE application previously filed and the FDA subsequently informed the sponsor that the product was a significant-risk device.

The FDA has now determined that the sponsor violated IDE regulations governing clinical studies involving investigational devices, as described below.

Inadequate information and review
The warning letter alleges that the sponsor provided misleading information on the risk assessment of the VCS. In doing so, it interfered with the investigator’s ability to protect the rights, safety and welfare of subjects under his care and the institutional review board’s (IRB’s) ability to conduct appropriate review of the study.

The risk evaluation provided by the sponsor stated that, “the [VCS] and the FDA licensed biologic (fibrin plug) do not present a potential for serious risk to health, safety, or welfare of a subject.” However, the sponsor failed to state that the proposed used of a particular fibrin sealant in the VCS was not an approved use and that the product was not a “licensed biologic” for this use.

Furthermore, the approved labelling for the fibrin sealant identified a number of risks that would be expected to be present when the sealant is used investigationally with the VCS device. However, the sponsor failed to provide information about these risks and did not disclose them in the informed consent form, even though they were identified by the manufacturer.

FDA denied access
On three occasions in May and August 2006, the FDA specifically requested that the sponsor provide accurate, complete and current information about the VCS study. However, the sponsor failed to do this and also declined to participate in a meeting with the FDA in July 2006.

Federal regulations require sponsors to grant access to permit authorised FDA employees – at reasonable times and in a reasonable manner – to enter and inspect any establishment where devices are held or where records of results from the use of devices are kept.

On 12 October 2006, an FDA inspector went to the sponsor's address listed in the IDE application. He was unable to gain entry. The following day he returned and was informed that the Chairman of the parent company maintained an office at the location but resided elsewhere. The FDA inspector called the Chairman and left an answer-machine message requesting a return call. However, the phone call was not returned. The FDA inspector attempted to access the premises again but was unsuccessful.

The sponsor of a trial involving a significant-risk medical device – who provided misleading information and failed to allow the FDA access to its premises for inspection – has been found to have violated Investigational Device Exemption (IDE) regulations. Jane Baguley reports.
visit the Florida address of the sponsor contact listed in the IDE application, but again could not gain access. Three days later, the FDA inspector left a voice message requesting a return phone call. On 17 October, the FDA inspector was directed to speak to another representative. The FDA inspector and his supervisor contacted that representative and were informed that the sponsor had submitted a letter to the FDA on 16 October withdrawing the IDE application previously filed.

Although the sponsor withdrew the IDE application, regulations require that records of the investigation are maintained for a period of 2 years following the date on which records are no longer required for the purposes of supporting a pre-market approval application.

At the time of writing the warning letter, the sponsor had not permitted the FDA access to its premises or to records pertaining to the VCS. The warning letter requested that the sponsor identified the location of the establishment where the VCS products were held and where records were maintained, so that the FDA may inspect and copy records in accordance with the applicable regulations. The letter also requested the sponsor to identify immediately any clinical investigators who have conducted, or are currently performing, clinical studies involving the VCS in the USA, as well as any IRBs that have reviewed these studies.

Source: [www.fda.gov/foi/warning_letters/s6354c.htm](http://www.fda.gov/foi/warning_letters/s6354c.htm)

---

**News in brief**

**Is the FDA failing to oversee clinical studies?**

In a report released at the end of September, the Inspector General of the US Department of Health and Human Services claims that the FDA does little to ensure the safety of the millions of people who participate in clinical trials. The report, entitled *FDA’s Oversight of Clinical Trials*, goes on to state that

- federal health officials do not know how many clinical trials are being conducted
- less than 1% of trial sites in the USA are audited
- where inspections do take place, it is long after the studies have been completed.

The Office of Inspector General received a congressional request to review the FDA oversight of clinical trials after a series of news articles highlighted vulnerabilities. The investigation aimed to determine the extent to which the FDA conducted inspections of clinical trials over a 5-year period and to assess the FDA’s processes for inspecting clinical trials.

The investigation revealed that the FDA has only 200 inspectors - some of whom only audit clinical trials part-time - despite having an estimated 350,000 testing sites to oversee. Worryingly, on those occasions when an inspector identified a serious problem, their initial findings were downgraded by drug officials in Washington almost 70% of the time. Among the remaining cases, the agency almost never followed up with an inspection to determine if the corrective action that had been demanded was actually implemented.

The report also highlights that clinical trials are subject to different rules depending on who pays for them: the FDA only oversees the safety of trials performed by sponsors (typically pharmaceutical companies) seeking approval to market their drugs or medical devices, and the Office for Human Research Protections oversees trials that are financed by the government. Privately financed non-commercial trials have no federal oversight at all.

The investigation also revealed that between 2000 and 2005 the FDA only disqualified trial investigators 26 times and disqualified their data just twice, despite the agency finding serious problems at trial sites 348 times during this period. The report concludes that the FDA’s oversight of clinical trials is disorganised and underfinanced, criticisms that have also been levelled at other FDA functions, including its oversight of foreign drug manufacturers and the safety of older medicines. In each case, the size and complexity of the tasks facing the agency have grown enormously in recent years, while the number of inspectors needed to complete these tasks has generally declined.

The report makes five recommendations to improve the FDA’s oversight of clinical trials:

- the development of a comprehensive clinical trials database to identify and target more effectively ongoing clinical trials for inspection
- the creation of an institutional review board (IRB) registry, to provide the FDA with basic information about IRBs that will enhance the agency’s ability to target IRBs for inspection

Source: [www.fda.gov/foi/warning_letters/s6354c.htm](http://www.fda.gov/foi/warning_letters/s6354c.htm)
UK’s Gene Therapy Advisory Committee releases annual report

The Gene Therapy Advisory Committee (GTAC) was set up in 1993 to advise on the ethical acceptability of proposals for gene therapy research on humans, with respect to the scientific merits and the potential benefits and risks of that research. GTAC also provides advice to Health Ministers in the UK on developments in gene therapy research. GTAC is the only research ethics committee in the UK empowered to approve clinical trials of gene therapy products; under the Clinical Trial Regulations of 2004, it is required to provide an ethical opinion on applications for the use of products meeting the definition of gene therapy medicinal products within 90 days of receipt of a valid application.

GTAC publishes an annual report detailing its activities in the previous year. Its current report summarises the activities undertaken in 2006:

- GTAC considered 14 applications to conduct gene therapy clinical trials in the UK, approving or conditionally approving all of them
- the majority of applications (eight) focussed on cancer; but there was a marked increase in non-cancer applications – particularly those to treat single gene disorders or infectious diseases – compared with previous years.

The report also summarises all the UK gene therapy trials since 1993, stating that GTAC has considered 138 applications, that 112 trials have gone ahead and that approximately 1300 patients have been recruited into these trials.

The primary concern of GTAC is whether a research proposal meets accepted ethical criteria for research on human subjects. However, the responsibilities of the Committee extend to providing advice for applicants on the:

- content of proposals for gene therapy research on human subjects
- design and conduct of the research
- facilities necessary for the proper conduct of the research
- arrangements required for long-term surveillance and follow-up.

GTAC’s responsibilities also extend to receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

- the clinical status of the subjects
- the scientific quality of the proposal
- the scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely
- whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable
- sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject)
- the potential benefits and risks to the subject of the proposed research.

Other activities

During 2006, GTAC agreed a Memorandum of Understanding with the Medicines and Healthcare products Regulatory Agency (MHRA) and the Central Office for Research Ethics Committees, which should enable the smoother sharing of information between all parties. GTAC also contributed comments to the following four consultations:

- two from the European Medicines Agency on inadvertent germ line transmission of vectors and environmental risk assessments
- one from the Health and Safety Executive on the use of genetically modified microorganisms
- one from the MHRA about the recommendations following the TGN1412 Phase I trial at Northwick Park Hospital.

Latest version of PDUFA widens authority of FDA

As reported extensively in the newsletter, on 27 September the US House and Senate passed the FDA Amendments Act of 2007 (FDAAA) into law. The FDAAA included the long-awaited 5-year renewal of the Prescription Drug User Fee Act of 1992 (PDUFA III), which took effect just 3 days before the previous legislation was due to expire.

PDUFA first became law in 1992. It allowed the FDA to collect fees from pharmaceutical manufacturers seeking approval for a new drug or biological agent. PDUFA was originally introduced in an effort to reduce the backlog of applications on file at the FDA and to shorten the period of time from initial submission to FDA decision. The first reauthorisation of PDUFA – PDUFA II – expanded the original goals of the legislation to include activities related to the investigational phases of a new drug’s development, and to increase FDA communication with the industry and consumer groups. PDUFA III authorised additional activities in both the preclinical and post-approval stages of drug research and development. PDUFA IV takes these powers a stage further.
The impetus behind the current legislation was again the significant period of time taken by the FDA to approve New Drug Applications and Biologics License Applications, a problem that the FDA attributed to limited resources. Thus, much of the text of PDUFA IV relates to estimates of the fees to be collected by the FDA in each of the next 5 years, the various waivers that may apply and how the resulting income will be used.

Section 103, Authority to Assess and Use Drug Fees, outlines the anticipated user fees for 2008, which should approach US$400 million, depending on the FDA’s workload (compared with US$305 million in 2007). It also details drug user fees for post-approval safety programmes. Section 104 relates to the fees payable for the review of television advertising for prescription drugs. Previously, pharmaceutical companies were able to submit their direct-to-consumer television adverts voluntarily to the FDA for review; however, there was no compulsory associated fee. PDUFA IV enables the FDA to collect a fee that will be used to help the agency finance its resource needs.

Section 105 explains the nature of the reports that the FDA will prepare each financial year to document its progress towards its published goals. The reports will also include information on how the agency has implemented its new authority for the collection of fees and how the fees have been used.

Source: <www.fda.gov/oc/initiatives/HR3580.pdf>

Critical advice offered to EMEA

In an article published recently in the British Medical Journal, Silvio Garattini (Director) and Vittorio Bertele (Head of the Regulatory Policies Laboratory) of the renowned Mario Negri Institute for Pharmacological Research in Milan, Italy, offered some advice to the European Medicines Agency (EMEA). They stated that, “Despite the undoubted advantages of the establishment of the European Medicines Agency criticisms have been made, mostly about its independence and transparency and the evaluation criteria”. One area particularly criticised by the investigators was the European pharmacovigilance system: the authors believe that the EMEA should establish a new pharmacovigilance committee, and that decisions to restrict the use of a drug or to withdraw it from the market should be made by an independent group.

Other suggestions included the following:

• the EMEA should follow the FDA’s lead with regard to non-inferiority trials
• more independent research by non-commercial trials should be performed as part of the development process of new medicines
• more data (eg. on toxicology) should be made publicly available by drug companies
• patents could be prolonged in exchange for “better, safer, more trustworthy, and more affordable innovation”.