CQAdvisor
A NEWSLETTER FOR THOSE WHO CARE ABOUT THE QUALITY OF CLINICAL TRIALS
ISSN 1367-076X
29 MAY 2001

IN THIS ISSUE 78

Electronic and paper versions available

FDA releases interim rule for paediatric trials

On March 30 the FDA released an interim rule for the "Additional safeguards for children in clinical investigations of FDA-regulated products." This has been issued in response to the increased number of paediatric trials performed as a result of the 1997 Modernization Act and the 1998 Pediatric Rule. The interim rule also intends to bring FDA regulations in compliance with the Children's Health Act of 2000. The interim rule mainly addresses the role of IRBs and is open for public comment. Details of the document will be published in a future newsletter.

Source: http://www.fda.gov/OHRMS/DOCKETS/98fr/042401a.htm

New guidance on financial disclosure issued by the FDA

Concerns about the potential bias in clinical studies caused by financial conflicts of interest led to a regulation on financial disclosure in the USA. This also affects foreign studies to be used to support a marketing application in the USA.

The FDA published a final rule on financial disclosure on 2 February 1998 (21 CRF Part 54). This was amended on 31 December 1998. The rule came into force 2 February 1999. Draft guidance on the rule was issued by the FDA on 26 October 1999. This guidance was amended in a new document issued on 20 March 2001.

Anyone who makes a marketing application (MA) of any drug, biological product or device must submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting covered studies. Failure to do so may result in the FDA refusing to file the application.

The latest guidance is summarised in this issue of *CQAdvisor*.

Summary of the 2001 Guidance on Financial Disclosure

This article by Professor David Hutchinson summarises the most important requirements of the FDA's March 2001 financial disclosure guidance. The regulation 21 CFR 54 applies to both US studies and those conducted elsewhere, like Europe, when the data is to be used in a marketing application in the USA.

Which studies are affected?

The rule requires applicants to either certify the absence of certain financial interests of clinical investigators or to disclose any specified financial interests for any covered study completed on or after 2 February 1999. Special circumstances apply for studies completed before this date.

A covered study is any clinical study in an MA:

- that the applicant or FDA relies on to establish that the product is effective
- in which a single investigator makes a significant contribution to the demonstration of safety.

In general this does not include Phase 1 (human pharmacology) studies or large open studies conducted at multiple sites. Applicants can check with the FDA if a study should be considered a 'covered study'.

The study does not have to be one conducted in the USA under an IND. Those in other countries are 'covered' if it is to be part of the MA in the USA.

A study *in vitro* using human specimens (eg. *in vitro* diagnostics) is a covered study if it is used to support an MA.

Who is involved?

A clinical investigator is a 'listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. These are the persons who actually conduct or take responsibility for an investigation or are team leader. In the USA it is simply those persons who: sign an FDA Form 1572; are identified in initial submissions or protocol amendments under an IND; or are identified as an investigator in a new product application (NDA, BLA). For non-IND studies the investigator should be identified by the sponsor.

The term also applies to the spouse and each dependent child of the investigator.

Others involved in the trial, for example nurses, office staff and those who provide ancillary or intermittent care are not included under the definition of clinical investigator.

Multicentre studies

Multicentre studies are covered clinical studies even though large numbers of investigators may each have recruited only a small number of subjects. Applicants may seek waivers but the FDA is unlikely to grant any such request for a multicentre study started after 2 February 1999.

How should the disclosure be made?

Certification or disclosure is required at the time of making the marketing application.

Applicants of marketing authorisations must submit to the FDA a list of clinical investigators who conducted covered studies. FDA Form 3454 should be used for all clinical investigators who have no financial conflicts of interest. A blanket certification may be made for investigators with nothing to disclose. Form FDA 3455 must be used for investigators where information needs to be disclosed.

The forms should be signed by a responsible corporate official or representative of the applicant (eg. chief financial officer). The applicant bears the responsibility for compliance even though they may have not been fully involved in

page 3 ►

◄ page 2

the trial (eg. a study sponsored by an academic institution or a contact research organisation).

Where financial conflicts of interest do exist the applicant must to inform the FDA of any steps taken to minimise the potential for bias.

Where the applicant has been unable to obtain relevant information from the investigator they must certify that despite the applicants due diligence they were unable to obtain the information and why it was unobtainable. The applicant must make sure that they can demonstrate that they expended an appropriate amount of effort in trying to collect the information.

It is not necessary to submit updated information after an application has been made but applicants should retain complete records.

How and when should information be collected?

The sponsor of a trial should obtain sufficient information to allow a complete certification/disclosure before allowing an investigator to commence a study. This allows the sponsor to assess any potential problems. The sponsor should also require the investigator to promptly update this information if any changes occur during the investigation and for the one year after study completion. The sponsor can consult the FDA at this early stage if they have any concerns about a particular investigator.

Information can be collected by any method. Most use a questionnaire. No elaborate tracking systems are required.

What should be disclosed?

The following items need to be disclosed for covered studies ongoing or completed after 2 February 1999:

- Compensation made to the investigator where the value could be affected by study outcome.
- A proprietary interest in the tested product (eg. patent, trademark, copyright, licensing agreement).
- Any equity interest in the sponsor of a covered study (eg. ownership interest, stock options) where value cannot be obtained by reference to public prices. Where the investigator holds interests in the sponsor's parent company this must also be disclosed.
- Any equity interest in a publicly held company that exceeds 50,000 US dollars in value, excluding those in mutual funds. This applies during the period of the trial and one year following completion of the study. Completion means all subjects have been enrolled and primary endpoint data on all subjects has been completed in accordance with the protocol (for that part of a continuing study). Specific details about the size and nature of any qualifying equity has to be disclosed. Holdings below the threshold need not be disclosed until their value exceeds 50,000 dollars. Falls in equity values need not be reported.
- Significant payments of other sorts (SPOOS) with a cumulative monetary value of 25,000 US dollars or more made by a sponsor to an investigator or his/her institution in a covered study. This does not apply to costs of conducting the clinical study or other clinical studies. It does include payments such as honoraria, consulting fees, grant support for laboratory activities and equipment not required for trial conduct or money to buy this equipment (eg. computers). This applies to payments made on or after 2 February 1999.

Contract research organisations (CROs)

The CRO involved in a covered trial must be aware of the relevant parts of the Investigational New Drug (IND, or IDE for a device) regulations. If the CRO is the sponsor, or it has been contracted by the sponsor to do so, it should follow 21 CFR Part 312.53 (or Part 812.43 for devices) and collect information about financial interests. If an investigator has a financial interest in the CRO and the CRO provides material support for the study the financial interest should be disclosed.

page 4 ►

◄ page 3

Trials by academic institutions

If a trial has been conducted by an academic institution without any support from a commercial sponsor, but then used by an applicant to support an MA, the academic institute is defined as the sponsor and has no equity interest to report. However, if the institution has any proprietary interest (eg. patent, copyright) then disclosure would be required.

Investigators' travel expenses

Reasonable expenses for travel made by an investigator including transportation and lodgings need not be tracked/reported. However, if the investigator is provided with 'lavish' travel (eg. flown to a resort location and stays on for additional vacation) then this needs to be disclosed. Those expenses incurred by the investigators' spouse or dependent children are considered unnecessary and would also need to be disclosed as SPOOS.

Possible FDA actions

In the light of disclosed information, the FDA may: initiate an inspection; request the applicant to submit further analyses to evaluate the effect of a certain investigator; request that further independent studies are performed; disregard the data from the covered study. FDA considers it unlikely that it will have to refuse to file an application due to these requirements.

Our advice for trial sponsors

- Keep detailed and complete records.
- Have a detailed SOP on this topic.
- Collect information for all studies unless the sponsor is convinced it will never be used for a US application.
- Collect information before the study starts – perhaps at the site selection/inspection phase.
- Update records regularly and submit the required information at the time of the application.
- Continue to update records for investigators who are conducting ongoing trials. Remember to collect information for one year after study completion.
- Discuss any concerns with the FDA on particular matters about financial disclosure.

Financial information for the purposes of disclosure can (and will) be inspected during an FDA audit. Inspectors have the authority to have access to and copy relevant documents. Therefore it may be appropriate to generate and keep the following documents:

- Questionnaires used to collect information
- Correspondence on the subject of financial disclosure, mail receipts, etc.
- For SPOOS, cheque stubs, records of electronic transactions, invoices, receipts may be relevant.

Our advice for investigators

Collection of financial information is now part of the clinical trial process. Try to be as helpful as possible, even though you may find some of the information to be disclosed personal and inappropriate. Failure to disclose important information may lead to your data being rejected by the FDA. Raise any objections or concerns you have with the sponsor before the study starts. Keep the sponsor updated about any changes in financial circumstances for one year after the end of the trial. Remember that information is required about your spouse's and dependent childrens' potential financial conflicts of interest. The sponsor and FDA will keep the investigator's private information confidential. FDA will only make public any financial information if they feel public interest clearly outweighs privacy.

Source: the new guidance is available on the FDA website: <http://www.fda.gov/oc/guidance/financialdis.html>. The forms FDA 3454 and 3455 can be obtained from the FDA website at: <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>

Consistent audit plan needed for global trials

A global clinical trial is performed using sites in different countries or regions in the world, from which the data will ultimately be included in several regional regulatory submissions. These trials can be difficult to perform due to cultural differences and a lack of consistency. It is advisable both before the trials commence and throughout their conduct that personnel are trained in study-specific global SOPs.

Consistency within a global trial is important. Consistent results can be obtained if methodology is standardised. Similarly it is important that there is a global audit plan in place to ensure a consistent QA approach at all sites.

Sites selected for audit will normally consist of trial naïve sites,centres in countries that have not previously been audited, experienced sites and those contributing a large patient population.The audit plan should also take into account the possibility that an unsceheduled audit may be required as a result of problems raised in monitoring reports.

Selecting the most appropriate auditor to carry out a site visit is important.An auditor must have good communication skills - both verbal and written. This is particularly important where the mother tongue of the auditees is different from that of the auditor.

Auditors must appreciate that in different countries the documents may have different names and certain procedures may differ. On a practical level, when discussing a specific document it is useful to show the auditee the actual document to prevent any confusion.

The auditor must have a presence and demand respect.This can be problematic in some countries where women are not regarded as professionals.

The verbal report delivered to the auditees must be well balanced illustrating both the good and bad points observed during the audit. In the more inexperienced sites the auditor may have a double role as an educator, a task requiring patience and clarity.

To improve consistency, it is often useful to perform the audit with auditors from different countries.This allows auditors to build on each other's strengths and experiences.

During the audit it is important to be aware of cultural and political issues surrounding the trial. The auditor should ensure that all the necessary personnel are invited to a preliminary meeting before the audit begins. It is very easy to cause offence by failing to invite a member of staff who is entitled to attend.

In some countries the patients own their medical records and they are therefore not stored at the trial site.This can cause problems for auditors and monitors alike when trying to perform source data verification.The problem needs to be discussed and addressed in the protocol.

In a global trial the auditor will encounter many different methods of performing the trial.Auditors must remember that different is not wrong and adapt to the circumstances presented.An example is in some Asian countries a chop or seal is used instead of a hand written signature, different but certainly not wrong.

Source: Good Clinical Practice Journal *Vol 7 No 4 April 2001 p 16-19*

One stop shop for key documents: <www.canarybooks.com>

Our website <www.canarybooks.com> is now a source for key documents.
Already on the site you will find pdf versions of the lastest financial disclosure guidance, the EU Directive on GCP in Clinical Trials (2001/20/EC) and the UK's latest guidelines on the content and format of patient information sheets.The site will be updated as new documents become available.

News *in brief*

Patient ADR reporting in UK?

Health Which? is urging the UK Medicines Control Agency (MCA) to consider the introduction of patient ADR reporting. The current 'yellow card' system only allows doctors and pharmacists to report ADRs. In contrast, the FDA accepts ADR reports from consumers. Health Which? feel that problems are arising in the UK due to "gross" under-reporting by doctors. The MCA does not accept reports from consumers because medical interpretation of the suspected reaction can be vital. Also, the agency cannot deal with the high volume of reports that would be generated.

Source: Scrip, *Issue No 2634, April 2001, p 4*

Information access in Japan

New Freedom of Information legislation came into effect in Japan on 1 April 2001 allowing outside individuals and organisations to request the disclosure of previously restricted documents. This will include documents relating to pharmaceutical regulatory affairs held by the Ministry of Health, Labour and Welfare. Requests for information can be made through 1,800 government sites nationwide. The government has up to 30 days to respond.

Source: Scrip, *Issue No 2634, April 2001, p 18*

Same day release of CPMP opinions

From 1 April, opinions released by the EMEA Committee for Proprietary Medicinal Products (CPMP) will be published on the day of their adoption rather than 15 days later. The Committee for Veterinary Medicinal Products (CVMP) will publish opinions two weeks after their adoption, rather than the eight week delay previously in place.

Source: European Regulatory Affairs News *Issue 108 March 2001 p 7*

Higher budget set to increase number of FDA inspections

President Bush has asked US Congress to increase FDA's drug and biologics programme budget by 9.5% for the fiscal year running from 1 October 2001. The money will be used to increase the number of full time employees from 9,219 to 9,611 and to improve surveillance of drug trials and imports. The agency's post marketing surveillance of adverse events will be expanded and the number of site inspections will rise by 33% (375 inspections).

Source: Scrip, *Issue No 2634, April 2001, p 14*

CQA advisor

Principal Author & Editor: Prof David Hutchinson

Senior Writer: Vicky Putt

Publications Manager: Paul Williams

Correspondents:

Gitte Raaschou Beck (Denmark)
Eugen Chicevic (Central Europe)
Paul-Etienne Chipp (Switzerland)
Bettina Klesse (South Africa)
Leny Aiach Telles Correa (Brazil)
Donna Cullen (USA)
Jorge Cúneo (Argentina)
Valerie Fletcher (UK)
Francois Geelen (Germany)
M Khurram Zaki Khan (Pakistan)
Lisbeth Tofte Hemmingsen (Denmark)
Joris Bannenberg (Netherlands)
Pamela Charnley Nickols (UK)
Jean-Michel Andrieux (France)
Kym Prieto (Europe)
Paul Chester (Europe)
Fabio Camarri (Italy)
Irene Herod (UK)
Ilian Ivanov (Bulgaria)
Mikhail Kandalov (Russia)
Hisashi Uematsu (Japan)
Paul Marcus (UK)
Alexey Melkov (Russia)
Volker Peinke (Germany)
Marc Robin (Germany)
Sam Tong (UK)
Maria Galikova (Slovakia)
Nigel Dent (UK)
Cecil Nick (UK)
Sheelagh Corcoran (UK)
Laura Brown (UK)
Clive Jenkins (UK)
Hideki Fujiwara (Japan)

Contact us by e-mail: editor@cradvisor.co.uk

Literature regularly reviewed includes:

QA Journal	*JRSM*
QUASAR (BARQA publication)	*Pharmaceutical Review*
Clinical Trials Advisor	*Scrip*
Applied Clinical Trials	*The Times*
MCA Eurodirect publications	*EFGCP Newsletter*
CRFocus	*AIOPI Newsletter*
GCP Journal	*The Statistician*
The Monitor	*MAIL*
Pharmaceutical Physician	*NLN Newsletter*
DIA Journal	FDA Warning Letters
Bulletin of Medical Ethics	*ESRA Rapporteur*

Web sites regularly reviewed includes:

EMEA, EFPIA, FDA, MCA, IFPMA,ICH, DGIII (European Commission)

Aims & Scope:

- to publish news and information about the results of GCP audits and inspections in the ICH regions
- to provide news, views and opinions about ICH GCP implementation
- to provide answers to readers' CQA questions and the views of inspectors
- to summarise and make readers aware of relevant articles and information in other publications, press releases and information on the Internet
- to provide information about meetings, conferences, training courses and publications.

Published by: Canary Ltd, PO Box 9, Guildford, Surrey GU2 7GY, UK
Telephone: 07000-CANARY (226279) or +44 1483 295910
Fax: 07000-FAXBACK (329222) or +44 1483 295911

Design: LIMA Graphics, Frimley, Surrey, UK
Print: Surrey Litho, Great Bookham, Surrey, UK