EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

DRAFT

Draft guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice

June 2006

1. INTRODUCTION

Directive 2001/20/EC[1] and Directive 2005/28/EC[2] provide principles of Good Clinical Practice that must be applied to all clinical trials that fall within the scope of the directives. Both directives acknowledge the specifics of non-commercial clinical trials that are conducted by researchers without the participation of the pharmaceutical industry, in particular with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indications. Recital 11 of Directive 2005/28/EC foresees that it might be unnecessary to apply certain of the details of Good Clinical Practice to suit the specific context of individual "non-commercial trials" arising in part through the conditions under which the studies are conducted. It also provides reference to existing simplified procedures that may facilitate but are not specific to non-commercial trials.

Sponsors and investigators conduct a wide range of clinical trials without the participation of the pharmaceutical industry including those aimed at the assessment of interventions with medicinal products used in the promotion of health, the prevention and/or treatment of disease and in rehabilitation and long-term care. Typically these clinical trials are for:

- Potential treatments for rare diseases;
- Comparative effectiveness as optimal-use trials; and
- Paediatric trials with medicinal products authorized only for adult patients.

Some non-commercial funders also support early-phase clinical trials, usually focusing on areas of healthcare where the prospects of commercial return are limited or not immediately apparent.

Non-commercial sponsors commonly study the "effectiveness" of a medicinal product compared to alternatives, which is of key importance to patients, health professionals and organisations seeking to improve clinical practice. In patients with chronic disease, these clinical trials may be designed to determine effectiveness over long periods requiring extensive follow-up.

2. LEGAL BASIS AND PURPOSE

According to recital 11 of Directive 2005/28/EC the Commission is asked to prepare a draft with guidance for the specific modalities for the non-commercial clinical trials.

Article 1(3) of Directive 2005/28/EC provides that Member States may introduce "specific modalities" in order to take into account the specificity of "non-commercial clinical trials" as far as Chapter 3 – 'Manufacturing or Import

[1] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJ L 121 1.5.2001 p. 34.

[2] Commission Directive 2005/28/EC of 8 April 2005 laying down the principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products OJ L 91 9.4.2005 p.13.

Authorisation' and Chapter 4 – 'Trial Master File and Archiving' of that Directive are concerned.

Article 1(4), first sub-paragraph, of Directive 2005/28/EC provides that Member States may take into account the special position of clinical trials whose planning does not require particular manufacturing or packaging processes, carried out with medicinal products with marketing authorisations within the meaning of Directive 2001/83/EC[3], manufactured or imported in accordance with the same Directive and conducted on patients with the same characteristics as those covered by the indication specified in the marketing authorisation

This guidance note provides guidance on "specific modalities", that is specific applications of the details of Good Clinical Practice, which Member States may introduce to take account of the specific needs of "non-commercial clinical trials", in particular in relation to manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file and on criteria for classifying such trials as "non-commercial".

3. NON-COMMERCIAL CLINICAL TRIALS

3.1. **Criteria**

"Non-commercial clinical trials" are clinical trials conducted by researchers without the participation of the pharmaceutical industry, for that reason the following criteria may be followed to define non-commercial clinical trials:

3.1.1. Characteristics of the sponsor:

- The sponsor should be a university, a hospital, a public scientific organisation, a non profit institution, a patient organisation or a researcher;
- The ownership of the data of these trials should belong to the sponsor listed in the first bullet point;
- No agreements between the sponsor and third parties allowing them to use the data for regulatory or marketing purposes should be in place; and
- The design, conduct, recording and reporting of the clinical trial should be under the control of the sponsor.

3.1.2. Characteristics of the clinical trial:

- The studies should not be part of the development programme for a marketing authorisation of a medicinal product.

The sponsor should consider the criteria carefully before indicating the non-commercial status of the sponsor in Section B.3.2 of the application form. If any of the criteria change during the conduct of the clinical trial so that the status of

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ L 311 28.11.2003 p.67. Directive as last amended by Directive 2004/27/EC OJ L 136 30.4.2004 p.34.

clinical trial is no longer non-commercial, the sponsor should inform the competent authority of the relevant Member State(s) and the Ethics Committee(s) as a substantial amendment. This might result in the clinical trial no longer being considered as a "non-commercial trial" for the purposes of Directive 2005/28/EC and therefore may require the sponsor to amend his working procedures.

Sponsors of non-commercial clinical trials should carefully consider whether their data is ever likely to be used for regulatory purposes e.g. to support a new indication for a marketed medicinal product. In particular, if some of the source data has only been retained for 5 years as required by the Directive 2005/28/EC, they may no longer be available for inspection when the application is made and therefore would not be in compliance with provisions of Directive 2001/83/EC.

Supplying an investigational medicinal product free or at reduced cost, and/or providing support in a limited way should not be taken to imply that industry is "participating" in the clinical trial for the purpose of Directive 2005/28/EC. Such support should not disqualify the clinical trial from being regarded as a non-commercial clinical trial. However the support should be notified to the concerned Ethics Committee and/or to the competent authority of the Member States.

4. SPECIFIC MODALITIES

In accordance with Article 1(3) of Directive 2005/28/EC a sponsors may apply following requirements in non-commercial clinical trials of human medicinal products. Nevertheless, any provisions for specific modalities must ensure that the objectives of the protection of the rights of patients who participate in a clinical trial, as well as the correct application of good clinical practice principles in general, are achieved.

4.1. **Investigational Medicinal Products with a marketing authorisation**

Where those medicines are used as an investigational medicinal product in a clinical trial in accordance with the marketing authorisation and legislation in the Member State concerned, access can be on the same basis as when they are used for routine treatment (i.e. local supply chain).

4.2. **Information relating to investigational medicinal products**

4.2.1.1. Simplified investigational medicinal product dossier

Sponsors may benefit from guidance on a Simplified Investigational Medicinal Product Dossier (IMPD) in section 4.1.6.2 and Table 1 of the Community guidance on applications to the competent authority[4]. The guidance allows an abbreviated dossier for trials with certain types of investigational medicinal product. For example, when an investigational medicinal product is to be used in a clinical trial in accordance with a marketing authorisation in the Community, the summary of product

[4] Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial CT-04-EN October 2005.
http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/10_05/CA_14-2005.pdf

characteristics (SmPC) should generally be sufficient in place of a full investigational medicinal product dossier or investigators brochure (IB).

4.2.1.2. Cross referral to another sponsor's investigational medicinal product dossier

When a competent authority already holds an investigational medicinal product dossier for a product, its owner may give permission to a sponsor to cross-refer to it. The sponsor should submit a letter with his application for a clinical trial authorisation from the owner of the investigational medicinal product dossier permitting the concerned competent authority to refer to his dossier as part of the application from the sponsor. The letter should also indicate that the sponsor would have access to the relevant pre-clinical and clinical data to the extent necessary for the oversight and safety monitoring of the clinical trial to be performed under his responsibility.

4.3. **Traceability and labelling of investigational medicinal products**

The aims and principles of traceability of investigational medicinal products are provided in Article 15 of Directive 2003/94/EC[5]; detailed guidance is provided in Annex 13 of the EU Good Manufacturing Practice guide[6]– "Manufacture of investigational medicinal products". The procedures should provide for labelling of an investigational medicinal product and documentation of its handling, storage, and dispensing as well as evaluation of compliance, which will contribute to the credibility of clinical trial data.

According to Article 1(3) of Directive 2005/28/EC a specific modality related to handling of investigational medicinal products where provisions laid down by Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) are not practicable may be accepted. Therefore, a sponsor may put in place arrangements with the pharmacist and the investigator to ensure, as far as possible, that specific accountability procedures and records for the trial been adopted. This includes documentation in the patient's medical chart or other source document, e.g. the patient's diary, and/or the case report form. The pharmacy's and the investigator's procedures and records should allow adequate re-construction of investigational medicinal product movements and administration, having regard to the purpose of the trial. It should at least include a procedure to record which patients received which investigational medicinal products during the trial with an evaluation of the compliance.

Labelling contributes to patient safety by documenting that subjects were provided with and used the investigational medicinal products in accordance with the protocol, as well as helping to evaluate the quality of the data produced.

[5] Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicines for human use and investigational medicinal products for human use. O.J.L262 p. 22

[6] Rules Governing Medicinal Products in the European Union. Eudralex Volume 4: Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm

Article 14 of Directive 2001/20/EC defines specific modalities for the labelling of an investigational medicinal product intended for clinical trials with the following characteristics:

- The planning of the trial does not require particular manufacturing or packaging processes;
- The trial is conducted with medicinal products with a marketing authorisation, within the meaning of2001/83/EC, manufactured or imported in accordance with the provisions of Directive 2001/83/EC, in the Member States concerned by the study,
- The patients in the trial have the same characteristics as those covered by the indication(s) specified in the above-mentioned authorisation.

Section 32 of Annex 13 of the EU Good Manufacturing Practice guide states that, for clinical trials described in Article 14 of Directive 2001/20/EC (described above), the labelling of the original container should include the following:

- Name of sponsor, contract research organisation or investigator
- Trial reference code allowing identification of the trial site, investigator and trial subject.

When a clinical trial is conducted with a marketed product there may be conditions in which re-labelling for trial purposes may be adapted, for instance:

- Where the trial protocol defines the treatment in terms of active substance only and does not specify the trade name of each product (i.e. for a reference medicinal product). In some protocols, these treatments are identified by only the ATC code;
- In the case of ambulatory trials (outpatients) when investigational medicinal products are supplied from the local supply chain (community dispensing pharmacies).
- When re-labelling may undermine the objective of the trial. For instance, some trials of standard care of a medical condition require a doctor to prescribe a medicine and a Community pharmacist to dispense it. In this situation, where the investigational medicinal product being tested in the clinical trial has the characteristics described in Article 14 of the Directive (see above), and it is dispensed from batches labelled in accordance with the requirements of a marketing authorisation (Directive 2001/83/EC re-labelling would be outside normal standard of care and might interfere with the objective of the trial.

In the following situations, certain specific labelling may be unnecessary or may be adapted:

- Where an authorized product is reconstituted/diluted prior to use under the supervision of a pharmacist in a pharmacy of a hospital, health centre or clinic linked to a clinical trial site, then the standard instructions for that product should be followed, and the preparation recorded. This applies also where several products are mixed for a single infusion or injection (which should be within usual practice for these authorised products). If the products are locally sourced from the pharmacy and the preparation is

local and for administration to the patient, the source marketed product(s) do not need to be relabeled.

- When the investigational medicinal product does not need particular handling and is administered under direct supervision of the investigator or investigator's team (e.g. infusion) adapted procedures for on-site documentation (such as recording the batch number), may be established.

4.4. **Documentation**

According to Article 1(3) of Directive 2005/28/EC Member States may introduce specific modalities relating to documentation on non-commercial clinical trials. The sponsor remains responsible for ensuring that all clinical trial information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified while protecting the confidentiality of records of the trial subjects as required by Article 5 of Directive 2005/28/EC.

4.4.1. Procedures for documentation and archiving

Article 15(5) of Directive 2001/20/EC requires the Commission to adopt and revise detailed guidelines on the documentation that relates to a clinical trial, which includes the master file on the trial, archiving, qualification of inspectors and inspection procedures to verify compliance with the Directive. The Commission set out these detailed guidelines in its Directive 2005/28/EC. Chapter 4 gives detailed guidance on archiving and the trial master file, which consists of the essential documents which enable both the conduct and the quality of the data produced to be evaluated. Additional guidance on the content of these documents in Volume 10 of the Rules Governing Medicinal Products in the EU[7].

It is the responsibility of the sponsor to consider whether a trial will or may be included in a marketing authorisation application and to take the necessary steps to ensure appropriate retention of essential documents.

For trials that are not to be used in marketing authorisation or pharmacovigilance submissions, essential documents should be retained, according to Article 17 of Directive 2005/28/EC, for at least five years after completion of the trial or for a longer period if required by the applicable regulatory requirement(s) or by agreement with the sponsor.

Normally all essential documents should be retained. However for certain types of non-commercial trials, including trials with medicinal products that have a marketing authorisation in the Member State concerned, a sponsor may wish to combine certain documents provided the individual elements are identifiable. Annex A provides illustrations of situations where this may be appropriate.

[7] Recommendation on the content of the trail master file and archiving. Volume 10 EudralexCollection http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

Annex A

Guidance on interpretations of Trial Master File requirements in clinical trials for non-commercial trials

Title of document	Inclusion in Trial Master File[8]
Investigator's Brochure (IB) Investigator's Brochure updates	An IB may not be required for trials of marketed products. When a SmPC is submitted to the competent authority instead of an IB, this and any updates should be included in the Trial Master File.
Financial aspects of the trial	In the case that there is no financial arrangements between the investigator and the sponsor in a non-commercial trial it is recommended that this be noted in the Trial Master File.
Curriculum vitae and/or other relevant documents evidencing qualification of investigator(s) and supporting trial staff Curriculum vitae for new investigator(s) and supporting trial staff	Depending on the nature of the trial and the extent of delegation by the principal investigator confirmation that an investigator or supporting trial staff has a recognised specialist appointment may be sufficient. Associates are under the supervision of the PI, who takes responsibility for their work at the clinical site. A list of approved associates, with their title (MD, nurse…) and their duties in the study should be kept in the Trial Master File if necessary and is all that is required.
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol.	Many medical/laboratory/technical procedure(s) and/or test(s) will be carried out by hospital laboratories; these laboratories should retain this documentation. Expected normal values and/or ranges for the trial should be specified in the protocol. If there are differences in the normal ranges between laboratories these should be documented in the Trial Master File if necessary. All updates should be included in the protocol with reference to the change in the Trial Master File.
Medical/laboratory/technical procedures/tests Updates of medical/laboratory/technical procedures/tests	Many medical/laboratory/technical procedure(s) and/or test(s) will be carried out by hospital laboratories; these laboratories should retain this documentation. Many Member States have national systems for quality control for hospital laboratories and the certification/accreditation will be part of the national quality assurance programme. If this applies, it is recommended that it be noted in the Trial Master File.
Master randomisation list	This may be a programme rather than a list and be held by the trial statistician. In that case the Trial Master File would document the parameters used in the programme.
Instructions for handling of investigational product(s) and trial-related materials	Many non-commercial trials use pharmacy supplies of medicinal products that have a marketing authorisation and the storage and dispensing instructions will be part of the pharmacy's standard operating procedures for handling clinical trial materials. If this applies, provided the pharmacy SOP conforms to the applicable legislation and guidance, including retention of records, it may be noted in the Trial Master File.
Shipping records for investigational product(s) and trial-related materials Documentation of investigational product(s) and trial-related materials shipment	Many non-commercial trials use pharmacy supplies of medicinal products that have a marketing authorisation and so the tracking of product batches, shipping conditions and accountability will be part of the pharmacy's standard operating procedures for clinical trials. If this applies, provided the pharmacy SOP conforms to the applicable legislation and guidance, including retention of records, this

[8] Essential documents listed as required to be located in the files of the sponsor(s) can instead be located in the files of the investigator or the Co-ordinating Centre for the trial, subject to agreement of the sponsor(s) and according to the agreed distribution of the sponsor's responsibilities. However the sponsor remains responsible for these documents in accordance with Chapter 4 of the GCP Directive.

Title of document	Inclusion in Trial Master File[8]
	may be noted in the Trial Master File.
Certificate(s) of analysis or batch release certificate of investigational product(s) shipped Certificate(s) of analysis for new batches of investigational product(s)	Many non-commercial trials use pharmacy supplies of medicinal products that have a marketing authorisation and so information about the investigational product(s) will be part of the pharmacy's standard operating procedures for clinical trials. Provided the pharmacy SOP conforms to the applicable legislation and guidance, including retention of records, it may be noted in the Trial Master File.
Pre-trial monitoring report	Some non-commercial trials involve investigators and sites that the sponsor judges that a pre-trial monitoring visit to be unnecessary to some or all of the sites. This should be recorded in the Trial Master File. Signed confirmation/agreement letters can also be used to verify that a site has suitable facilities to carry out the trial and should be kept in the Trial Master File.
Trial initiation monitoring report	Some non-commercial trials involve investigators and sites that the sponsor judges a trial initiation monitoring visit to be unnecessary to some or all of the sites. This should be documented in the Trial Master File. In some cases investigator training meetings are held prior to the trial starting, so a trial initiation visit may not be necessary. Signed confirmation/agreement letters can also be used to verify that trial procedures have been understood and should be included in the Trial Master File.
Monitoring visit reports	The determination of the extent and nature of monitoring should be based on considerations such as the objective, design, complexity, size, etc, of the trial.
Investigational products accountability at site	Information about the use of investigational products according to the protocol is often collected on Case Report Forms (CRFs) in non-commercial trials. If this applies provided the pharmacy SOP conforms to the applicable legislation and guidance, including retention of records, it may be noted in the Trial Master File. In some trials, detailed recording of drug accountability will be necessary.
Documentation of investigational product destruction	If this applies, provided the pharmacy SOP conforms to the applicable legislation and guidance, including retention of records, it may be noted in the Trial Master File. For some trials the need for reconciliation between medicinal products supplied, used and returned before destruction will require specific detailed recording if not covered by the pharmacy SOP.
Final trial close-out monitoring report	Confirmation/agreement letters can be signed to verify that all activities related to trial close-out are completed and that copies of essential documents are held in the appropriate files and that a site visit is not required. If this applies, it is recommended that it be noted in the Trial Master File.