

LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS

This paper discusses labelling requirements for investigational medicinal products (IMPs) used in clinical trials which come under the requirements of Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 which implement the Directive and came into force on 1 May 2004.

- **In the UK, where a clinical trial involves a marketed medicine used within its marketing authorisation, the product can be labelled in accordance with the requirements for a dispensed medicine.** The relevant aspects and make up of such labels are shown in section A below.
- **Guidance on the requirements of IMPs in other situations is given in [Annex 13](#) of the EU's good manufacturing practices documentation.** This is shown in the other sections of this note.

A sample or description of the labelling to appear on each IMP when supplied to the patient in the trial is to be provided as part of the request for the Clinical Trial Authorisation (Paragraph 12 of Part 2 of Schedule 3 to the Medicines for Human Use (Clinical Trials) Regulations 2004). The style examples provided in this note may be able to help in this regard.

There may be other items with pharmacological effects used in a trial, but which are not IMPs. These should be labelled in accordance with good practice for the type of product concerned.

A. Marketed products in circumstances as set out in the second paragraph of Article 14 of the Directive¹

In this situation (where the trial involves a medicine marketed in the UK used within its marketing authorisation) Regulation 46 (2) of the Clinical Trials regulations provides for labelling according to normal dispensing labelling requirements. Regulation 46 (2) refers to Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994; the section of that Schedule relating to labelling of "dispensed relevant medicinal products" (ie following a prescription) is shown in Annex A attached. (Although this

¹ Article 14 (second paragraph) of the Directive points to adapted provisions for labelling IMPs 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, in the Member States concerned by the study, a marketing authorisation, manufactured or imported in accordance with the provisions of Directive 2001/83/EC
- the patients participating in the trial have the same characteristics as those covered by the indication specified in the above mentioned authorisation.

Schedule has been amended for other reasons, the Annex A extract is unchanged).

In addition the cautionary label “Keep out of the reach of children” is a legal requirement on all UK dispensed medicines. Information on this and other cautionary and advisory labels for dispensed medicines is given in Appendix 9 of the British National Formulary.

Thus the normal dispensing label required would take the form of this exemplar:

Product name, form and strength	
Directions [as specified by the prescriber]	
Patient name	Date of dispensing
Name + address of hospital/primary care supplier	
Keep out of the reach of children [Any additional cautionary label (as recommended by the British National Formulary)]	

(although the quantity of dosage forms (tablets, capsules etc) is generally also added for dispensed medication).

However for consistency with other countries (eg to allow for single sourcing of supplies) sponsors of commercial trials may wish their products be labelled following the guidance in [Annex 13](#) for this type of trial. This is set out in paragraph 32 of [Annex 13](#), and requires that the following particulars be added to the original container (but not obscure the original labelling):

- (i) name of sponsor, contract research organisation or investigator;
- (ii) trial reference code allowing identification of the trial site, investigator and trial subject.

The original labelling on a marketed product would contain information on the product, usage and storage conditions, batch number etc.

If this alternative is followed in a publicly-funded trial, it would be appropriate to add to the original pack’s existing label:

- (i) the name of the investigator;
- (ii) a code, eg the EUDRAct number for the trial, the name and address of the pharmacy etc supplying direct to the patient to indicate the trial site; and
- (iii) code for the trial subject – in practice publicly-funded trials would normally include the patient’s name on the supply, so the code would be additional.

It would be normal good practice to add the date of the supply.

The labelling of the original EU marketed product would have to follow other legal requirements. The additional label would look similar to a dispensing label (see below). Labelling in this manner (in association with the product's existing labelling) would therefore be consistent with UK Regulation 46 (1).

Trial [EUDRAct number]	
Investigator: Dr XXXXXXXXXXXX	
Patient name and identification code	Date of supply
Name + address of hospital etc supplier	

B. Marketed products which are to be used outside of its licensed indications in a clinical trial

This section relates to trials which go beyond the boundary of the circumstances set out second paragraph of Article 14 of the Clinical Trials Directive, but still use marketed products, which would already be made to Good Manufacturing Practice standards. Such products would need to be labelled in compliance with UK Regulation 46 (1), which specifies labelling in accordance with Article 15 of the GMP Directive 2003/94/EC.

Article 15 of the GMP Directive states: "Labelling. In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product."

Guidance on the labelling that would meet these requirements is given in the EU's Good manufacturing practices, [Annex 13](#) on Manufacture of investigational medicinal products (July 2003). Paragraph 26 (and the summary at Table 1) of that Annex² set out the information that should be included on labels, unless its absence can be justified (eg use of a centralised electronic randomisation system).

The items listed in paragraph 26 of [Annex 13](#) are given in the first column of the table at Annex B below, with commentary given in the second column.

² Other paragraphs in the labelling section of Annex 13 require that the particulars should appear in the official language(s) of the country in which the IMP is to be used (paragraph 28), or give guidance about what to do when outer packaging and the immediate container are intended to remain together (paragraph 29), where the immediate container is a blister pack or small unit such as an ampoule (paragraph 30), permissive use of pictogram or additional information (paragraph 31), or when changing the use-by date (paragraph 33).

From the table in Annex B, it can be seen that many of the required items are already included on the label of the original pack of the marketed medicine, or would be normally included on a dispensing label. Thus it is suggested that a label similar to, but a variation on, the normal dispensing label can be added to the original pack of the product to complete the labelling requirements. This would take the form as follows:

For Clinical Trials Use Only	
Trial Name	
For use in trial [give directions for use or as directed in patient information leaflet for the trial]	
Trial [EUDRAct] number, name [of investigator and sponsor]	
Patient name and identification number	Date of supply
Name and address of supplier	
Keep out of reach of children [if not already on pack, but not added where the product is not taken home by the patient]	

As stated above, such a label needs to be affixed to the original pack of the marketed product without obscuring the existing labelling information.

In **placebo controlled trials** it would be necessary to present all supplies in consistent packaging to maintain blinding, with consistent labelling also. If the original product's marketing authorisation holder is prepared to provide packs of the matching placebo, the company is also likely to agree to provide them in similar containers and with consistent labelling with the marketed product. In other circumstances consistency is likely to be best achieved through repackaging and full labelling as noted in the next section below.

C. Novel IMPs/placebo products

For novel IMPs, the full labelling as set out in paragraph 26 of [Annex 13](#) would need to be complied with. This would be an assembly operation which would need to be undertaken as part of manufacturing by a unit with an IMP Manufacturing Authorisation, and to comply with GMP standards. Directions for use can be given through use of a leaflet or other explanatory document intended for the trial subject or person administering the product (see item g in the table above); this may be of particular help where dosages may need to be varied during the course of the trial.

In trials which include a placebo, the placebo itself is an IMP which needs to be manufactured to GMP standards, and would be expected to take the full labelling as in the table above (ie [Annex 13](#) paragraph 26). For consistency to preserve blinding, the active product would also need to take the same full labelling.

Note on Labelling operations

Adding patient specific labelling to a marketed product is part of dispensing in supplying to a patient. However it is an assembly operation where labels are prepared and attached in bulk in advance. There appear to be the following options associated with such labelling in advance:

- Where a trial involves a series of separate dosage changes it would seem preferable to repack and label in an IMP manufacturing unit to provide for Good Clinical Practice.
- Where a trial only uses a consistent dosage through out the trial, and there are large numbers of patients in the trial at a single centre, it would be efficient to pre-assemble labelled supplies in the hospital (or health centre) making use of the exemption provisions of Regulation 37, leaving the individual patient details to be added as a dispensing operation.

May 2004. The above is based on the work of a Medical Research Council/Department of Health Joint Project to codify good practice in publicly-funded clinical trials. Anyone reading these notes is invited to comment on what clarifications would help with the practical implementation of the new legal requirements.

Extract from Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994

Dispensed relevant medicinal products

3. – (1) Subject to the following provisions of this Schedule, where a relevant medicinal product is a dispensed relevant medicinal product the container of that product shall be labelled to show the following particulars –

- (a) the name of the person to whom the product is to be administered;
- (b) the name and address of the person who sells or supplies the product;
- (c) the date on which the product is dispensed;
- (d) where the relevant medicinal product has been prescribed by a practitioner, such of the following particulars as he may request –
 - (i) the name of the relevant medicinal product or its common name;
 - (ii) directions for use of the relevant medicinal product; and
 - (iii) precautions relating to the use of the relevant medicinal product,

or, where a pharmacist, in the exercise of his professional skill and judgement, is of the opinion that any of the particulars are inappropriate and has taken such steps as in all the circumstances are reasonably practicable to consult with the practitioner but has been unable to do so, particulars of the same kind as those requested by the practitioner as appear to the pharmacist to be appropriate.

(2) Where the container of a dispensed relevant medicinal product is enclosed in a package immediately enclosing that container the particulars set out in sub-paragraph (1) may be omitted from the container if that package is labelled to show such particulars.

(3) Where a number of containers or packages, or of containers and packages, of dispensed relevant medicinal products all of the same description are enclosed in a package, sub-paragraph (1) (d) shall be deemed to have been complied with if such of the particulars referred to in that sub-paragraph as would, apart from this sub-paragraph, be required to be shown on each container or package, or on each container and package so enclosed, are shown on either one of more such containers or packages or such containers and packages as the case may be.

Annex B

Annex 13 labelling requirements	Comments
(a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);	Annex 13 paragraph 27 allows that the address and telephone number of the main contact for information etc need not appear on the label where the subject is given a leaflet or card which provides this detail and has been instructed to keep this in their possession at all times. However this would not seem to cover the need for the name of the sponsor, CRO or investigator. This could be combined with the trial reference code in item (d)
(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;	This information would be included on the label of the marketed product itself
(c) the batch and/or code number to identify the contents and packaging operation;	This information would be included on the label of the marketed product itself
(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;	The obvious trial reference code would be the EUDRAct number, the site could be identified by the normal hospital pharmacy address label. It would appear useful to group the name of the investigator and sponsor with this information (see (a) above)
(e) the trial subject identification number/treatment number and where relevant the visit number;	Patients would normally expect to see their name on a dispensed product's label, but in this case would need to include their identification number as well. Visit number may be relevant if different products or dosages are supplied at separate visits according to the protocol. However where marketed products are used in a trial such medication changes during the course of the trial may not be so frequent.
(f) the name of the investigator (if not included in (a) or (d));	See comment on (d) above.
(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);	It is understood that standard directions for use are likely to be set out in an information leaflet provided to the patient. "Use as directed" would not be sufficient in a clinical trial.
(h) "For clinical trial use only" or similar wording;	This would need to be added.
(i) the storage conditions;	This information would be included on the label of the marketed product itself
(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity;	This information would be included on the label of the marketed product itself
(k) "Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.	This is a legal requirement for all dispensed medicines in the UK, and may already be included on the marketed pack.