

Position Statement on the packaging of oral cytotoxic medicines for clinical trials: July 2005

The development and rapidly expanding use of oral cytotoxics has advantages for patients and the NHS. For pharmacy services, however, it is important to understand that although there may be a reduction in the workload of a small team of specialist staff in the chemotherapy reconstitution unit, a very significant burden is shifted to a larger number of non-specialist staff in very busy dispensaries. A robust framework for management of the potential risks to staff and patients is essential. These wider aspects of safe practice with oral chemotherapy are more fully addressed elsewhere ⁽¹⁾.

Where licensed packs of a cytotoxic drug are used outside the context of a clinical trial, blister or strip packed products should *always* be purchased in preference to loose tablets/capsules.

This position statement relates to the presentation, packaging and labelling of oral cytotoxic drugs specifically for patients in clinical trials. It should be drawn to the attention of all relevant pharmacy staff including dispensary managers and those with specific responsibility for clinical trial support.

- Most oral cytotoxics are presented as coated tablets or capsules. While most present a minimal exposure hazard to staff (or patients/carers), the chance of accidental skin contact should still be minimised.
- ***Tablets/capsules should therefore normally be obtained only in blister or strip packs.***
- Ensuring appropriate packaging of clinical trials supplies can be particularly difficult. This must be considered at the earliest possible stage of trial design. In addition, the importance of agreeing appropriate dispensing procedures should be drawn to the attention of sponsors and investigators. ⁽²⁾
- Whilst it is unusual for medicines custom-packed for trial use to include a Patient Information Leaflet, the importance of giving patients comprehensive information about their medicines remains unaltered. Where a licensed medicine is used in a clinical trial (as the subject or comparator), appropriately over-labelled licensed packs including a PIL should always be used in preference to unlicensed packs without a PIL.
- However, it must also be remembered that the use of unbroken patient packs may itself pose risks to patients if, as a result, patients are given more doses than are needed for the intended course of treatment. The decision about whether or not to issue only unopened packs should therefore be based on a documented local risk assessment.
- ***For proposed new studies, loose tablets and capsules should be accepted only in very exceptional circumstances (such as Phase 1 studies) and by specific agreement with senior pharmacy staff, following a documented local risk assessment.***
- Where use of loose tablets or capsules is unavoidable, skin contact through handling must be minimised. Manipulations which are not essential for clinical reasons, such as reconciliation counts, should be avoided.
- A pragmatic approach to the continuing use of loose tablets/capsules for ongoing studies is recommended but it is the responsibility of the sponsors to enable a change to blister or strip packs as rapidly as possible.

- The Health & Safety and the clinical risks considered above may also apply to newer anti-cancer medicines which do not meet the traditional definition of “cytotoxic”. The range of medicines to which this guidance is to be applied locally should also therefore be determined by a risk assessment process.

Interim guidance on labelling of dispensed clinical trial medicines investigational medicines products

The standards to be applied to labelling of clinical trial medicines are listed below in a copy of paragraphs 26 – 33 of Annex 13 to the EU Guide to Good Manufacturing Practice ⁽³⁾.

Whilst this guidance applies specifically to Good **Manufacturing** Practice for Investigational Medicinal Products (GMPIMP), it is clear that for the purposes of inspection MHRA also regard this standard as applicable to Good Clinical Practice and to *dispensed* IMPs. MHRA expectations of how the detail is to be interpreted to ensure compliance will become clearer in due course. In the meantime, we believe that compliance can be achieved with minimal enhancements to accepted standards of good dispensing practice.

Some points in the text below have been emphasised by the use of italics *The italics do not appear in the official document*

Labelling

26. Labelling should comply with the requirements of Directive 91/356 as amended for Investigational Medicinal Products. The following information should be included on labels, ***unless its absence can be justified***, e.g. use of a centralised electronic randomisation system:

- (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 un-blinding);
- (b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;
- (c) the batch and/or code number to identify the contents and packaging operation;
- (d) ***a trial reference code allowing identification of the trial, site, investigator and sponsor*** if not given elsewhere;
- (e) ***the trial subject identification*** number/treatment number and where relevant, the visit number;
- (f) the name of the investigator ***(if not included in (a) or (d))***;
- (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);
- (h) "For clinical trial use only" or similar wording;
- (i) the storage conditions;
- (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.
- (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.

27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency un-blinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the immediate container and on the outer packaging ***(except for immediate containers in the cases described in Articles 29 and 30)***. Other languages may be included.

29. When the product is to be provided to the trial subject or the person administering the medication within an immediate container together with outer packaging that is intended to remain together, and the outer packaging carries the particulars listed in paragraph 26, ***the following information shall be included on the label of the immediate container*** (or any sealed dosing device that contains the immediate container):

- a) name of sponsor, contract research organisation or investigator;
- b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
- c) batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor ***if not given elsewhere***;
- e) the trial subject identification number/treatment number and where relevant, the visit number.

30. If the immediate container takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 26 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:

- a) name of sponsor, contract research organisation or investigator;
- b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
- c) batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor ***if not given elsewhere***;
- e) ***the trial subject identification*** number/treatment number and where relevant, the visit number;

31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

32. For clinical trials with the characteristics identified in Article 14 of Directive 2001/20/EC, the following particulars should be added to the original container but should 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.

33. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.

References :

1. Position Statement on safe practice and the pharmaceutical care of patients receiving oral anticancer chemotherapy, British Oncology Pharmacy Association, January 2004
2. Practice Guidance on Pharmacy Services for Clinical Trials, The Royal Pharmaceutical Society and The Institute of Clinical Research, June 2005
3. Annex 13 (revised July 2003) to the E.U Guide to Good Manufacturing Practice, the European Commission.