

GUIDANCE ON REPACKAGING AND OVERLABELLING SMALL BATCHES OF MEDICINES IN PHARMACY DEPARTMENTS

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GUIDANCE ON REPACKAGING AND OVERLABELLING SMALL BATCHES OF MEDICINES IN PHARMACY DEPARTMENTS

1. Introduction

There is an increasing demand for small packs of licensed medicines to be provided to clinics, day case units and Emergency/Urgent Care Departments with labels already attached, to allow issue against a prescription or under a Patient Group Direction without further pharmacy involvement.

The labels give patients instructions for use that have been specified by the prescriber for a specific patient group in accordance with local clinical governance policy. The labels have a space for the patient's name and date of issue to be added by the clinic staff. These medicines improve both efficiency and safety by allowing patients to be supplied with medicines that have been appropriately labelled when an on-site pharmacy service is not available.

The safest and most appropriate method for the repackaging and overlabelling of medicines is under GMP in an MHRA- licensed Pharmacy Specials manufacturing unit. However, there are a limited number of Specials units licensed to perform repackaging and overlabelling operations and therefore there is sometimes a need for small scale batches to be assembled in dispensaries.

2. Purpose and Scope

This document provides guidance on how repacking and overlabelling operations can be carried out in accordance with the principles of GMP in hospital pharmacies that do not hold a Specials Manufacturing licence from the MHRA. Such activities can be carried out under the professional exemption from licensing provided they are undertaken by or under the supervision of a pharmacist. Specific guidance for sites that hold a Specials licence is available from the MHRA and batch manufacture under a licence is outside of the scope of this document.

3. Principles for overlabelling and repackaging by the NHS

The following principles are established from the MHRA guidance (see appendix 3) and taking into account verbal MHRA advice to the NHS Pharmaceutical Quality Assurance Committee.

- NHS pharmacy departments may undertake batch repackaging and overlabelling subject to the following restrictions:
 - The limit for repackaging is a maximum batch size of 25 packs.
 - The limit for overlabelling is a maximum batch size of 100 packs.
 - There should be a limit of one batch per product per month prepared for stock.
 - The repackaging or overlabelling activity must follow Good Manufacturing Practice¹ (GMP) principles (see section 4 below) and must be performed by or under the supervision of a pharmacist

- Batch release must be by a pharmacist.
- Batch records must be kept (see 4.1 and 4.4 below).
- If a hospital pharmacy repackages or overlabels medicines for sale or supply **outside** its corporate body, to another hospital pharmacy, then it must be undertaken in a licensed facility which holds a Manufacturing Specials (MS) Licence, regardless of the quantities supplied.
- Repackaging is a more complex operation than overlabelling and is associated increased risk of errors during preparation. Packing into plain cartons reduces differentiation between products and therefore increases the risk of selection errors. If repackaging is undertaken, steps must be taken to minimise these risks. Wherever possible preference should be given to overlabelling original packs rather than repackaging.

4. Professional standards for repackaging and overlabelling in NHS pharmacies

These standards for the quality assurance of repackaging and overlabelling of medicines in NHS pharmacies have been developed by the NHS Pharmaceutical Quality Assurance Committee, based on the principles of GMP. They aim to support dispensaries in the preparation of small batches of overlabelled and repackaged medicines in a safe, accurate and practical way.

4.1. Quality Management

- 4.1.1. All repacking and overlabelling activities, including product release, should be clearly defined in Standard Operational procedures, recorded on worksheets (batch records) and performed in accordance with the requirements of Good Manufacturing Practice.
- 4.1.2. Any changes (to processes, procedure or documentation) should be planned and implemented through a documented change control process.
- 4.1.3. Records of all products repackaged and overlabelled must be retained for five years after release or for one year after the product's expiry, whichever is the longer, for audit and management purposes.
- 4.1.4. Errors should be recorded, reviewed, and any action taken to reduce risk of recurrence should be assessed to establish effectiveness and a record of this should be made.
- 4.1.5. Complaints about repacked or overlabelled medicines should be recorded and actioned according to local policy.
- 4.1.6. Any suspected defective medicines found as part of repacking or overlabelling operations should be reported in accordance with local procedures.
- 4.1.7. Any recall of repacked or overlabelled medicines should be actioned and recorded according to local procedures.

4.2. Facilities

- 4.2.1. Facilities or location of repacking and overlabelling operations should be appropriate, preferably a dedicated area where no other activity is carried out at the same time and away from areas in the main dispensary where mix-ups might occur.

- 4.2.2. Facilities for repackaging and overlabelling operations should be chosen to minimise the risk of errors and dust and dirt build up. N.B. Batch size may need to be limited by the space available.
- 4.2.3. Lighting, temperature, humidity and ventilation should be appropriate such that they do not adversely affect, directly or indirectly, the medicinal products during repackaging or overlabelling and subsequent storage. Storage and working temperatures should be monitored.
- 4.2.4. The work area should be organised to allow logical processing and adequate segregation of batches at all stages of the process.
- 4.2.5. Storage areas should be clean and dry and should be cleaned according to written procedures.
- 4.2.6. Equipment used during repackaging or overlabelling operations should be maintained, where required, and cleaned in accordance with local procedures to minimise the risk of cross contamination occurring.
- 4.2.7. Computer programs used to prepare documentation and labels should be password controlled.

4.3. Personnel

- 4.3.1. All staff involved in repacking or overlabelling activities should be appropriately trained.
- 4.3.2. Competency to carry out duties should be assessed initially, and a re-assessment programme should be implemented.
- 4.3.3. Responsibilities of all staff involved in repacking and overlabelling activities should be clearly defined:
 - assessing new product requests for repacked or overlabelled products including for clinical and technical appropriateness
 - preparing worksheets and labels
 - approving worksheets and labels
 - carrying out repacking and overlabelling activities
 - post-production checking of batches
 - releasing batches

4.4. Documentation and labels

- 4.4.1. A worksheet using a standard template should be used for all repackaging and overlabelling activities (see Appendix 1 and 2 for template examples). Product-specific worksheets should incorporate the master label for the product being prepared and both the worksheet and the master label must be approved by a pharmacist.
- 4.4.2. Worksheets should include
 - the dates of worksheet preparation, approval and review
 - the signature of the pharmacist who has approved the worksheet
 - details of the finished product to be prepared (product name (rINN), strength, dose form, pack size, batch size).
 - details of starting materials (packs of medicines; cartons; bottles; flag labels) including any expected overage.
 - details of any equipment required e.g. measuring vessels
 - instructions for repackaging or overlabelling (this may include label positioning, line clearance, in-process checks, and any necessary health and safety measures for handling hazardous medicines).

- space to record
 - overlabelling or repackaging batch number and date of preparation
 - batch and expiry details of packs used
 - signatures for assembly, repackaging and/or labelling and all pre- and in-process checks
 - signature and date of final approval and release by a pharmacist
- a reconciliation section to record the production and use of labels and PILs
- space for duplicate of all labels used
- comments section to record any deviations

4.4.3. A master label should be prepared for inclusion on each worksheet. Label design should ensure that critical information is easy to read.

Labels should contain the following information where appropriate:

- Generic name of the medicinal product
- Pharmaceutical form
- An indication of the active ingredients expressed qualitatively or quantitatively per dosage unit or for a given volume or weight
- The content of the container – number, volume or weight
- Route of administration
- Instructions for patient (including any special warnings)
- Storage instructions
- Batch number and expiry
- Contain the instruction “Keep out of reach and sight of children”
- Details of the hospital pharmacy
- Space to enter
 - patient details
 - date of issue

N.B. If the overlabelling or repackaging activity was undertaken in hospital pharmacy with a MS licensed unit, but not under the MS licence, the MS number must not appear on the label.

4.4.4. Master worksheets and labels must be subject to version control and access to amend them must be restricted to authorised personnel.

4.5. Processing

4.5.1. Repackaging and overlabelling activities should be organised to ensure a logical workflow, with assembly, processing, quarantine and release segregated either by space or by time.

4.5.2. The status of batches should be clearly labelled if they are stored at any stage during the preparation process (e.g. “Incomplete; awaiting further stock”, “awaiting final check” or “quarantine”).

4.5.3. Each batch to be prepared must be assigned a unique identifying batch number that is recorded in a logbook or secure electronic record.

- 4.5.4. Each batch should be prepared using a pre-approved product-specific worksheet (see section 4.4 above). Any amendments to, or deviations from, the worksheet must be checked and approved by a pharmacist.
- 4.5.5. Batch labels, including an additional label as a record for the worksheet, should be prepared from a product-specific master template. The number of labels produced should be recorded on the worksheet to allow label reconciliation and destruction of any un-used labels.
- 4.5.6. For repackaging exercises, additional PILs for each pack, plus one to be stapled to the worksheet as a record, should be duplicated from the original PIL in one of the original packs. Each duplicated PIL must be individually checked for print quality and to ensure all text fits within the margins. The number of labels produced should be recorded on the worksheet to allow label reconciliation and destruction of any un-used labels.
- 4.5.7. Wherever possible all the same batch of original product should be used (as this assists the audit process in the event of a recall).
- 4.5.8. Shelf lives should be assigned using the following principles:

Product type	Suggested shelf life
Overlabelled packs	Manufacturer's original shelf life
Products sealed enclosed in their original primary container (tablets and capsules in blister strip packaging, ampoules, vials)	Manufacturer's original shelf life
Loose tablets and capsules and liquids with no special storage requirements	Maximum 12 months from the date of repacking
Loose tablets and capsules with a desiccant or liquids with a stated shelf life on opening	Seek advice from manufacturer or Regional QA

- 4.5.9. Before beginning any stage of the process, a check should be performed to make sure there are no other medicines, labels or documentation in the work area to avoid any mix ups.
- 4.5.10. For temperature sensitive items, steps should be taken to minimise the time refrigerated items out of the refrigerator and being processed. If a specified time limit for time out of the refrigerator is given by the manufacturer this should be noted on the worksheet and the time that items spend out of the refrigerator should be monitored to ensure this is not exceeded.
- 4.5.11. An assembly check should be performed by a suitably trained member of staff before the products are repackaged or overlabelled.
- 4.5.12. For repackaged batches:
- The container and closure must be capable of maintaining the quality and integrity of the product over the allocated shelf life, and bottle caps should be child resistant unless otherwise requested. The containers and closures to use should be specified on individual worksheets.
 - Blister packs should not be cut or folded as this may affect the integrity of the product.

- The label should be attached to the product in such a way that it can easily be read. For very small containers, flag-labelling may be necessary: if this method is chosen, all of the text must appear on one side of the flag to ensure that it can be easily read.
- The PIL (original or copy) should be inserted into a carton or attached to the outside of the primary container using an elastic or cellophane band, in such a way that the label is still readable.

4.5.13. For overlabelled batches

- The overlabel should be placed on the space provided for a dispensing label or on any blank space. Care should be taken not to obscure any of the critical information that is not repeated elsewhere. If there is not a suitable blank area on the pack that can be used for labelling (e.g. if the container is small) this can be achieved by flagging labels onto the pack. Other options include using a number of smaller labels to convey the required information rather than trying to use one large standard label.
- The overlabel must not interfere with any FMD (Falsified medicines Directive²) features of the original pack. To conform with FMD requirements the tamper evident seal on the pack should not be broken, therefore the placement of a label on the primary container (e.g. tube of ointment, eye drop bottle) contained within an outer pack is discouraged. Units overlabelling products for use within their own hospital may open the pack in order to apply a label to the primary container, providing the pack is not sold or supplied to any other legal entity after the seals are breached.

4.5.14. The worksheet must be completed contemporaneously in indelible ink. Any alteration should have one line crossed through the incorrect information, the correction added, and the alteration should be signed and dated.

4.5.15. Any deviations or unexpected events should be recorded on the worksheet.

4.5.16. Finished product should be quarantined pending release by a pharmacist.

4.6. Product release

4.6.1. A formal recorded decision of batch release should be taken by a pharmacist.

4.6.2. The release check should include:

- Checking the label against master label
- Visual inspection of each finished product, including label positioning.
- For repackaged items, checking
 - Quantity and identity are correct
 - PIL is present and correct
- Checking that the batch has been prepared by suitably trained staff.
- Checking that the worksheet has been accurately completed
- Evaluating any recorded deviations

5. References

1. EU Good Manufacturing Practice
(see http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm)
2. The EU Falsified Medicines Directive (2011/62/EU)
(see <https://www.gov.uk/guidance/implementing-the-falsified-medicines-directive-safety-features>)
3. Guidance to the NHS on the Licensing Requirements of the Medicines Act 1968.
Medicines Control Agency, September 1992.
4. MHRA Questions & Answers for Specials Manufacturers, Revision 1, January 2015
(see <https://www.gov.uk/government/publications/guidance-for-specials-manufacturers>)
5. The Human Medicines Regulations 2012
(see <http://www.legislation.gov.uk/uksi/2012/1916/contents/made>)

Appendix 1 Template Overlabelling Worksheet

Template Overlabelling Worksheet					
Reference Code		Prepared By		Date	
Version Number	V1.0	Issued By		Review Date	

GENERIC NAME OF PRODUCT PHARMACEUTICAL FORM STRENGTH PACK SIZE	Trust/site:			
<ul style="list-style-type: none"> Use this worksheet to record the details of batch overlabelling activity in all bold-edged boxes Assign each batch a unique batch number 	Date of overlabelling	Batch size: (Max 100)	Pharmacy batch number:	Expiry date: (Original pack expiry)

1. ASSEMBLY

1.1. Starting materials (all starting material packs should have same BN)

Manufacturer name	Batch number	Expiry	Assembled by	Assembly checked by

1.2 Label preparation

- Print sufficient labels for each pack plus one extra for the worksheet. If extra labels need to be printed separately this should be documented
- Obtain check before affixing to this worksheet and proceeding with overlabelling

Master product label <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"> <p style="text-align: center;">Route of administration</p> <p style="text-align: center;">Product details (Pack size)</p> <p>Instructions for use</p> <p>Special warnings</p> <p>Patient name: _____ Date supplied: _____</p> <p>Supplied by: _____</p> <p style="text-align: center;">Keep out of the reach and sight of children</p> <p>Pharmacy name & address BN: XXXXX Expiry: MM/YY</p> </div>	Actual label	Total No. labels printed	
		Printed by	
		Checked by	

2. OVERLABELLING

<ul style="list-style-type: none"> Clear work area to prevent mix-ups with any other product (signature required) Check container for integrity of the seal Overlabel each container (signature required) <ul style="list-style-type: none"> Always label the outer pack Avoid covering critical information and Braille if possible. Use space provided by the manufacturer If there is insufficient space it is permissible to cover <ul style="list-style-type: none"> Company logo Brand name Barcode Keep out of reach and sight of children 	Confirm work area clear <div style="border: 1px solid black; height: 20px; width: 100%;"></div>
	Overlabelled by <div style="border: 1px solid black; height: 20px; width: 100%;"></div>

Template Overlabelling Worksheet					
Reference Code		Prepared By		Date	
Version Number	V1.0	Issued By		Review Date	

3. CHECKING AND PHARMACIST RELEASE					
<ul style="list-style-type: none"> Confirm identity and number of original packs and that each pack has been labelled Check label on 5 finished packs Complete label and pack reconciliation checks 	Packs		Labels		
	No. expected (A)	<input type="text"/>	No. printed (D)	<input type="text"/>	<input type="text"/>
	No. Rejected (B)	<input type="text"/>	Used on worksheet (E)	<input type="text"/>	<input type="text"/>
Batch released by Pharmacist (signature)	<input type="text"/>		No. Released (C)	<input type="text"/>	No. Destroyed (F)
Date	<input type="text"/>				Used on product (G)
			Reconciliation of packs	Reconciliation of labels	
			A = B + C	<input type="text"/>	D = E + F + G
				<input type="text"/>	<input type="text"/>

Appendix 2 Template Repackaging Worksheet

Template Repackaging Worksheet					
Reference Code		Prepared By		Date	
Version Number	V1.0	Issued By		Review Date	

GENERIC NAME OF PRODUCT PHARMACEUTICAL FORM STRENGTH PACK SIZE	Trust/site:			
<ul style="list-style-type: none"> Use this worksheet to record the details of batch repackaging activity in all bold-edged boxes Assign each batch a unique batch number Assign expiry date. Medicine supplied undamaged in the primary container (blister strip/ampoule/vial) can be given the manufacturers original expiry date. For loose tablets/liquids refer to local SOP or Regional QA guidance (maximum 12 months from date of repackaging). 	Date of repackaging	Batch size: (Max 25)	Pharmacy batch number:	Expiry date:

1. ASSEMBLY

1.1. Starting materials (all starting material packs should have same BN)

Manufacturer name	Batch number:	Expiry:	No. original packs:	No. cartons:	Assembled by:	Assembly checked by:

1.2 Label preparation

- Print sufficient labels for each pack plus one extra for the worksheet. If extra labels need to be printed separately this should be documented
- Obtain check before affixing to this worksheet and proceeding with repackaging

Master product label <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p style="text-align: center;">Route of administration</p> <p style="text-align: center;">Product details (Pack size)</p> <p>Instructions for use</p> <p>Special warnings</p> <p>Patient name: _____ Date supplied: _____</p> <p>Supplied by: _____</p> <p style="text-align: center;">Keep out of the reach and sight of children</p> <p>Pharmacy name & address BN: XXXXX Expiry: MM/YY</p> </div>	Actual label 	Total No. labels printed	
		Printed by	
		Checked by	

1.3 PIL preparation

- Print or photocopy sufficient PILs for each pack plus one for the worksheet (this should be the same version as the original pack). Original PILs may also be reused.
- Obtain check before proceeding with repackaging

<ul style="list-style-type: none"> Print or photocopy sufficient PILs for each pack plus one for the worksheet (this should be the same version as the original pack). Original PILs may also be reused. Obtain check before proceeding with repackaging 	No. PILs required (A)		PIL Count (A = B + C)	
	No. original PILs (B)		Produced by	
	No. PILs produced (C)		Checked by	

Template Repacking Worksheet					
Reference Code		Prepared By		Date	
Version Number	V1.0	Issued By		Review Date	

2. REPACKING

<ul style="list-style-type: none"> • Clear work area to prevent mix-ups with any other product (signature required) • Fold PILs to suitable size • Remove the product from the original container and count out the required amount • Add the required amount and 1 PIL to each plain carton and label. • Repeat for each original carton • Attach a copy of the PIL to the worksheet. 	Confirm work area clear
	Repacked by

3. CHECKING AND PHARMACIST RELEASE

<ul style="list-style-type: none"> • Confirm identity and number of original packs • Check label and contents of 5 finished packs • Complete PIL, label and pack reconciliation checks 	Packs		Labels		PILs	
	No. expected (D)		No. printed (G)		No. expected (K)	
	No. Rejected (E)		Used on worksheet (H)		No. original PIL reused (L)	
	No. Released (F)		No. Destroyed (I)		No. printed (M)	
	Reconciliation D = E + F		Used on product (J)		Attached to worksheet (N)	
			Reconciliation G = H + I + J		No. Destroyed (O)	
				Reconciliation K = L+M+N+O		
Batch released by Pharmacist (signature)						
Date						

Appendix 3: Regulatory Background and Definitions

MHRA guidance

In 1992 the MHRA (at that time called the MCA) issued a document called “Guidance to the NHS on the Licensing Requirements of the Medicines Act 1968”³. This provided guidance on the application of the licensing provisions in the Medicines Act 1968 and its secondary legislation, in particular those provisions governing the manufacture, preparation and distribution of medicinal products. At the time of writing, this document had not been withdrawn by the MHRA or superseded.

In addition, the MHRA has published “Questions & Answers for Specials Manufacturers”⁴ which clarifies that overlabelling and repackaging activities are assembly activities and therefore is a licensable activity unless certain conditions are met.

Definitions

The definition of “assemble” in relation to a medicinal product given in Section 8 of the Human Medicines Regulations 2012⁵ is: “includes the various processes of dividing up, packaging and presentation of the product, and “assembly” has a corresponding meaning”.

- **Repackaging**

For the purpose of this document, “Repackaging” is synonymous with “breaking bulk”, “pre-packing”, “repacking” or “packing down”.

It is defined as taking the pack of a licensed medicinal product, opening it to repack the contents, and labelling it with directions for use.

Usually repackaging operations involve the packing down of tablets from original packs into smaller lots, but it can be applied to other forms of medicine such as liquid preparations and may occasionally involve combining medicines to create a larger pack size.

- **Overlabelling**

Overlabelling is defined as the placing of a label onto the outer (secondary) packaging of a licensed medicinal product in a batch process. No other operation is undertaken to manipulate the licensed medicinal product in any other way.