



**PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

PI 028-1
13 January 2009

AIDE-MEMOIRE

**GMP INSPECTION RELATED
TO PACKAGING**

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1. DOCUMENT HISTORY

Adoption by Committee	31.10.2008
Entry into force of PI 028-1	01.03.2009

2. INTRODUCTION

- 2.1. The process of packaging of medicinal products is listed among the risk factors that may affect the quality of the finished medicinal products and may also cause mix-ups.
- 2.2. The increased number of the defects of medicinal products occurred due to deficiencies in the process of labelling and packaging has drawn inspectors' attention towards the need for identifying and clarifying the critical aspects of this specific stage of inspection, in order to have a uniform interpretation of the provisions of the current GMP guide concerning packaging of medicinal products and prevention of mix-up.
- 2.3. In the light of technological progress, considering the wide variety of medicinal products developed, the 2005 PIC/S Seminar (Bucharest, Romania) was dedicated to the GMP inspection of the final stage of manufacturing process (primary and secondary packaging, labelling).

This Aide-Memoire is the outcome from the 2005 PIC/S Seminar.

3. PURPOSE

- 3.1. The purpose of this document is to provide guidance for GMP inspectors in preparation for inspections. This document aims to define the minimal requirements acceptable for an inspector as well as the requirements that provide maximum safety for the finished product ("best practices").

- 3.2. The Aide-Memoire is the direct result of the 2005 PIC/S Seminar. The Aide-Memoire should enable the inspector to assess the GMP compliance of the packaging process using the quality risk management tools.

4. SCOPE

- 4.1 The following Aide-Memoire describes different areas which could be evaluated during the GMP inspection of packaging and labelling process. However, the Aide-Memoire should be considered as a non-exhaustive list of areas to be looked at during an inspection.
 - 4.2 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovation or the pursuit of excellence. The advice in this Aide-Memoire is not mandatory for industry. However, industry should consider PIC/S recommendations and Aide-Memoires as appropriate.
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5. AIDE MEMOIRE

	Area of operation/ Items	Notes	Crucial questions	Supporting documents
	Packaging materials			
1.1	Quality and purchasing	<ul style="list-style-type: none"> • purchasing from approved suppliers; • auditing the manufacturing sites of suppliers of primary packaging materials for sterile products (vials, rubber stoppers, syringes, etc.) and of printed materials; • compliance with specifications; • up-dating the documents (quality specifications), in accordance with the marketing authorization and any subsequent variations; • delivery from supplier made such as to preserve the quality (to prevent contamination). 	<ul style="list-style-type: none"> • What is the policy for suppliers' approval? • Show me the audit report • Do the primary materials specifications comply with the Pharmacopoeial parameters and limits? 	<p>GMP Guide 1.2 iv, 1.3 vii, viii, 5.40, 5.41, 4.2, 4.11</p> <p>Ph.Eur</p>
1.2	Receipt	<ul style="list-style-type: none"> • quality documents: certificates of analysis; • checking the conditions for packages shipment and handling; • integrity checks and identification of each batch of primary packaging material or printed material received; • de-dusting and cleaning of packages on the outside (separate area). 	<ul style="list-style-type: none"> • Show me the records and SOPs which apply when receiving primary packaging materials or printed materials • Describe internal labelling system 	<p>GMP Guide 5.27, 5.4, 5.3, 5.42, 5.43 4.19, 4.20, 4.21</p>

	Area of operation/ Items	Notes	Crucial questions	Supporting documents
1.3	Storage areas	<ul style="list-style-type: none"> • adequate capacity, order and organization, location plan available; • the cleaning status, procedure and records; • physically separated areas for “quarantine”, “approved”, “rejected/recalled” materials or a system that provides similar safety; • secured conditions (physically separated areas, controlled, authorised access) for storage of primary and secondary printed materials (cartons, labels, leaflets); • storage of one batch per pallet – when the number of recipients allows -, without mixing batches on the same pallet ; • storage conditions adequate to each category of materials (qualification of the ventilation, air conditioning unit, critical parameters monitoring – temperature, humidity); • existence of an efficient system to prevent entrance of rodents, insects or other animals; • adequate control over destruction of materials. 	<ul style="list-style-type: none"> • Show me the seasonal/annual trends and results of temperature and humidity monitoring • Show me the location plan and records concerning these activities 	GMP Guide 3.1 – 3.4, 5.5, 5.7, 5.28, 5.29, 3.18 – 3.23, 3.25
1.4	Quality control	<ul style="list-style-type: none"> • sampling plan and conditions, according to the material being sampled; • specific laboratory equipment for the testing of packaging materials; • testing of packaging materials/packages in accordance with the methodology approved in the marketing authorization (functionality tests according to the manufacturer specification and tests 	<ul style="list-style-type: none"> • Show me the sampling plan and records for primary packaging materials (including labels) • Show me the approved specification and current results from internal testing • Show me the certificates issued by QC for one or more of these materials / 	GMP Guide – Annex 8:1, 5, 3.40, 3.41, 6.1, 6.6, 6.17, 5.54, Annex 1: 91

	Area of operation/ Items	Notes	Crucial questions	Supporting documents
		<p>according to current edition of relevant pharmacopoeia);</p> <ul style="list-style-type: none"> integrity testing for primary packaging, differentiated for each category of finished products (when applicable); in-process controls with relevance for the quality of the primary packages used (weight, filling level, blister scan, leak test, verification of the printing of labels, bar code reader challenges); assessment of the integrity for a sterile product packaging. 	<p>packages used for primary packaging</p>	
1.5	Manufacturing premises (packaging area)	<ul style="list-style-type: none"> designed and built-up to minimise the risk of contamination and mix-up - enough space, logical positioning of packaging equipment, separation of each and every primary and secondary packaging line (different cleanliness levels); qualification (IQ, OQ, PQ) of utilities (HVAC, PW, WFI, sterile steam, inert gases used, if applicable); monitoring of environmental conditions based upon the nature of the product (sterile or non-sterile). 	<ul style="list-style-type: none"> Show me the qualification (IQ, OQ, PQ) of utilities used inside the primary packaging area Show me the results of environmental monitoring (especially for primary packaging of sterile products) How is the access ensured for products/ materials and personnel to production areas? 	GMP Guide – Annex 1: 5, 11, 12, 3.7, 3.8
1.6	Packaging equipment and process	<ul style="list-style-type: none"> high performance, qualified and well-maintained; equipment, able to ensure the control during the primary/secondary packaging; line clearance (working area, packaging lines, label printing machines and other equipments should be clean and free from any other products, materials or documents previously used); content of adequate level of details on the checklist for line clearance; 	<ul style="list-style-type: none"> Show me the SOP and records of the line clearance Show me the checklist used for line clearance IQ, OQ, PQ and CQ 	3.34–3.39, Annex 15 -19, 5.44-5.53, 5.55, 5.57, 5.38, 5.39

	Area of operation/ Items	Notes	Crucial questions	Supporting documents
		<ul style="list-style-type: none"> • line cleaning; • cleaning of dust extractors • checking of the type of label used and its attachment on the primary package; • the presence of safety elements of the package (to prevent the counterfeit); • validation of the packaging process (critical process operation) – protocol, report and records; • adequate functioning of electronic devices to establish identity, such as barcode or RFID readers. • waste handling 	<ul style="list-style-type: none"> • Show me the qualification/validation of the packaging equipment/process • Show me the calibration and maintenance records for the packaging line • Show me the SOP and program for mix-up prevention 	
1.7	Documents	<ul style="list-style-type: none"> • batch packaging records (BPR) – on paper or electronic form (attention paid to level of access, electronic signature, etc.) for every batch or sub-batch manufactured; • SOPs and instructions for reconciliation, especially for the printed materials (including investigation of any discrepancy noticed and solving before batch release); • defined and adequate action limits regarding reconciliation; • adequate control of return in storage area of excess packaging materials; • adequate and documented investigation of packaging process deviations. 	<ul style="list-style-type: none"> • How do you ensure the security of the data entry in the electronic BPR? • Show me the records of investigation of any discrepancies noticed during reconciliation? • How did you investigate the packaging process deviations? • Show me the SOP for handling the obsolete or damaged printed packages 	4.7 – 4.9, 4.16, 4.18, 5.56, 5.15, 5.39
1.8	Personnel	<ul style="list-style-type: none"> • adequate in terms of qualification and training regarding hygiene practices, clothing and operation on particular packaging equipments; • knows and applies the procedures regarding the activity performed; 	<ul style="list-style-type: none"> • Show me the records of medical checks for operators working in primary packaging area. • Observe and discuss with personnel involved in the packaging process, to see the 	2.1, 2.2, 2.5 vi, 2.7 – 2.10

	Area of operation/ Items	Notes	Crucial questions	Supporting documents
		<ul style="list-style-type: none"> performs operation reliably and with no impact on the quality of the product; training of maintenance personnel and contractors. 	<ul style="list-style-type: none"> level of their knowledge on the operations they perform Show me the records of training on line clearance SOP 	
1.9	Quality assurance	<ul style="list-style-type: none"> Quality policy, risk management, risk assessment self inspection system (frequency based on the critical aspects of packaging materials/ processes, taking into account the number and gravity of the quality defects and taking the appropriate preventive and corrective measures); investigation of complaints to identify the package/ packaging related cause; assessment of the change control impact on the package/packaging of the finished product, during the whole shelf life of the product; release procedure on printed and primary packaging materials; release procedure of printed and primary packaging materials 	<ul style="list-style-type: none"> Show me the self inspection plan and outcome How did you investigate the complaints related to packaging? 	9.1, 8.3, 8.6, Annex 15 – 43, 44

6. REVISION HISTORY

Date	Version number	Reasons for revision

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