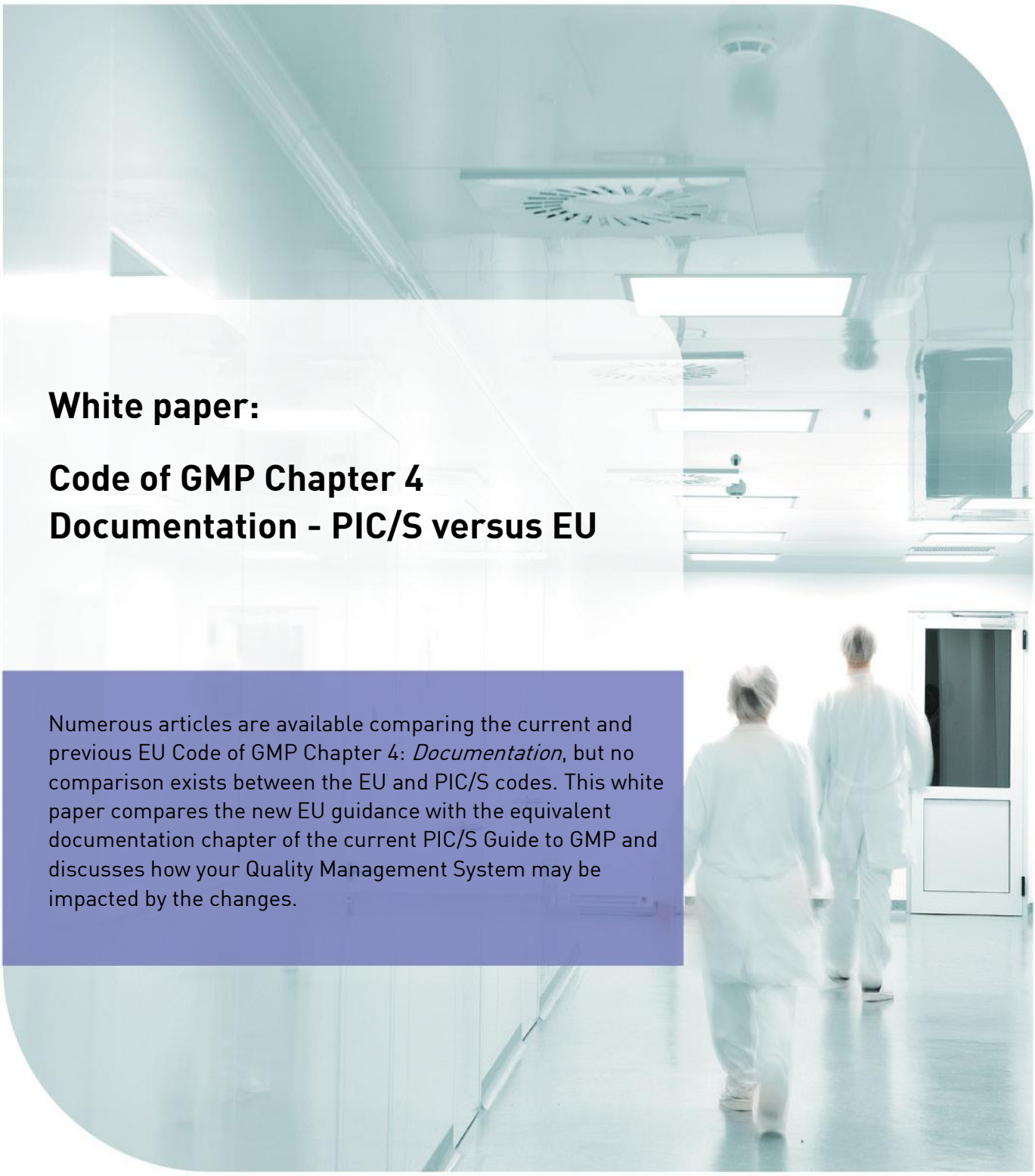

# White paper:

# Code of GMP Chapter 4 Documentation - PIC/S versus EU

Numerous articles are available comparing the current and previous EU Code of GMP Chapter 4: *Documentation*, but no comparison exists between the EU and PIC/S codes. This white paper compares the new EU guidance with the equivalent documentation chapter of the current PIC/S Guide to GMP and discusses how your Quality Management System may be impacted by the changes.

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# Introduction

Changes to the European Union (EU) Code of Good Manufacturing Practice (GMP) Medicinal Products for Human and Veterinary Use, Chapter 4: *Documentation*, came into operation on 30th June 2011.

The European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. GMP guidance from the EMA and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) are closely aligned and so the EU Code of GMP is relevant for Australia and other PIC/S aligned countries. Amendments to the EU Code of GMP are often the forerunner to changes that are then adopted within the PIC/S Guide to GMP for Medicinal Products. Consequently, the update to the EU documentation chapter is a good 'heads-up' of potential changes that may have future impact on your Quality Management System (QMS).

# Reasons for the change

In January 2011, the EU published an update to GMP Annex 11: *Computerised Systems* to align with current industry good practice and adopt a risk based approach (effective 30th June 2011). Consequent changes were then required for the EU Chapter 4, particularly with respect to electronic documentation.

## Differences between versions

The most recent version of the PIC/S Code of GMP (PE009-9) has not been adopted by the Australian Therapeutic Goods Administration (TGA) (PE009-8) but is operational in other PIC/S aligned countries. Consequently, it is important to note for the scope of this white paper that there is no difference in the current and previous versions of PIC/S Chapter 4. However, EU Chapter 4 has undergone substantial change with many details adopted from current GMP practices in the pharmaceutical industry.

The aim of this white paper is to compare EU and PIC/S codes and not differences between versions of the same code (available elsewhere). A cursory comparison between the different versions is therefore only included here for completeness.

| Code of GMP | Current Version | Previous Version | Chapter 4 Differences |
|---|---|---|---|
| PIC/S | PE009-9 | PE009-8 | None |
| EU[1] | Volume 4 | Volume 3 | Encompasses all forms of document media<br>Fully defined documents within the QMS<br>Different types of documents and their requirements<br>Retention periods<br>Line clearance<br>New developments around real-time release<br>Activities of the qualified person<br>More detailed list of processes requiring SOPs<br>Logbooks |

1. Taken from 'New EU GMP Guide Chapter 4 on Documentation' (14th Nov 2012) http://www.gmp-compliance.org/eca_news_2361_6724,6865,6730,6766,6768.html

# Comparison between the different codes

The content of both codes has very similar intent; a QMS compliant with the requirements of PIC/S Chapter 4 is likely to be compliant with most of the EU guidance clauses as well.

However, there are some differences where the EU guidance has additional requirements or gives further detail and/or clarification. These are listed under the following headings, with a comprehensive, clause-by-clause comparison between PIC/S and EU at the end of this white paper.

## Holistic compliance of the QMS

The *Principle* section of Chapter 4 in both the EU and PIC/S guidance outlines the general importance of documentation in ensuring overall compliance within the Quality Assurance system. The EU code indicates that good documentation is key to operating in compliance with GMP requirements and that;

> "The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products."

The EU guidance applies a stronger emphasis to the holistic compliance of QMS processes and the control and management of its documentation. This is in line with more recent trends within the pharmaceutical industry for companies to understand their manufacturing practices and processes as a whole, the overall process capability and risk, and implementing Quality by Design (QbD) principles to ensure product quality.

## Controlling electronic, hybrid and hardcopy systems

Both PIC/S and EU have requirements to ensure that all documentation is adequately controlled. Both codes indicate that document media includes paper, electronic documentation and photographic media. The EU also introduces the term "hybrid form", where some documentation elements exist as electronic and others as paper based (EU Clause 4.1; absent in PIC/S; refer to specific clauses in the comparison table at the end of this white paper). The following example illustrates different types of document media.

| Type of document media | Example |
|---|---|
| Hardcopy (paper based) | A hardcopy form is used to record written data with a written approval signature and filed in a compactus for the allotted retention period |
| Hybrid | An electronic form is completed online and then printed for a written approval signature and filed in a compactus for the allotted retention time |
| Electronic | An electronic form is completed online and is approved using electronic signatures; the data is securely managed and retrievable from backup media |

EU Clause 4.1 further indicates that:

- All document types within the QMS must be defined and adhered to
- Requirements apply equally to all media types
- Complex systems must be understood, well documented and validated with adequate controls in place
- Master documents, official copies, data handling and records must be stated for both hybrid and homogeneous systems
- Appropriate controls for electronic documents such as templates, forms and master documents should be implemented.

Much of the EU Clause 4.1 is implied within the PIC/S Chapter 4 but has not been as clearly detailed. Also, PIC/S Clause 4.9 is more focused on ensuring the accuracy and security of electronic records/data including:

- Record accuracy must be checked
- Only authorised persons should be able to enter/modify data
- Access should be restricted by a password or other means
- There should be an audit trail of changes and deletions
- The result of entry of critical data should be independently checked
- Electronically stored batch records must be protected by backup transfer on magnetic tape, microfilm, paper or other means

- Data must be available throughout the period of retention.

It should be noted that the requirements of PIC/S Clause 4.9 are covered by EU GMP Annex 11: *Computerised Systems*.

Documentation must be clear and unambiguous and structured in an orderly fashion to be compliant with either code. There are nuances in how this is expressed within the clauses and some differences between the codes. However, the general intent of both codes is that documents are written in a plain English style and are fit for purpose –that is, designed for the audience using them.

## Types of documents

The EU guidance divides GMP documentation into two major types – instructions and records/reports. Good Documentation Practices (GDP) are expected to be applied to all types of GMP documentation, including the site master file, not just specifications, manufacturing documents, procedures and records as per PIC/S (refer to the table below).

The EU guidance also stipulates that there must be an inventory maintained of documents within the QMS (EU Clause 4.32); this is not specified by PIC/S although it would be unusual not to find a master document list in the QMS of a company compliant with PIC/S. It is also typically one of the first documents an auditor asks to review.

The additional EU documents, not included in the PIC/S document types, need to be defined and formally managed within the QMS. This may be an area of your QMS that requires review – some companies do not control documents such as electronic templates, and the site master file or technical agreements may not appear in the master document list of the QMS.

| EU Document type | Example |
|---|---|
| Instructions (directions or requirements) | Specifications<br>Manufacturing Formulae, Processing, Packaging and Testing Instructions<br>Procedures (SOPs, Work Instructions, Methods)<br>Protocols<br>Technical Agreements |
| Records and reports | Records<br>Certificates of Analysis<br>Reports |
| Site Master File | A document describing GMP related activities of the manufacture. |

The QMS must also now formally document and record the following:

- Technology transfer
- Additional personnel matters such as signature lists, training in GMP and verification of training
- Change control
- Investigations into deviations and non-conformances
- Internal quality/GMP compliance audits
- Summaries of records where appropriate (e.g. product quality review)
- Supplier audits.

(Refer to EU Clause 4.29; this specific requirement is absent in PIC/S Chapter 4, however many of these documents are standard, best practice, Quality Systems typically seen in a QMS compliant with other chapters of PIC/S or ISO9001).

Both codes require documents to be free from errors, not hand-written, with suitable controls to ensure accuracy, integrity, availability and legibility. EU defines 'written' as recorded or documented on media from which data may be rendered in a human readable form. This definition captures both electronic and hardcopy systems and is in line with the recent changes to EU GMP Annex 11: *Computerised Systems*.

## Retention periods

Both codes require batch documents to be kept a year past the expiry of the batch. However, the EU guidance also:

- includes more detail for ensuring appropriate retention periods of a range of documents
- specifies that the controls for securing record integrity throughout retention should be validated where appropriate.

| EU document type | Recommended duration |
|---|---|
| Batch documentation excluding investigational medicinal products (IMPS) | One year after the expiry date or at least five years after certification of the batch by the Qualified Person (whichever is longer). |
| Batch documentation for IMPs | At least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used |

| EU document type | Recommended duration |
|---|---|
| Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation | Retained as long as the authorisation is valid. Documentation may be retired when superseded by a full set of new data, with documented justification for superseding and considering impacts to batch documents (e.g. Process validation raw data). |
| Other documents | Other requirements which are described in additional legislation might specify longer retention periods.<br>Depends on the business activity that the documentation supports |

**Note:** Refer to the detailed table below for a comparison between the EU and PIC/S code retention requirements.

## Acknowledgements of new developments

EU Chapter 4 acknowledges new electronic initiatives within the industry and provides some guidance regarding Process Acceptance Testing (PAT) or real time release. Electronic batch records may report compliance summaries and exception/out-of specification (OOS) data reports only. This is only appropriate if the process is validated and continuously monitored and controlled. Where robust electronic controls are in place, there may also be justification for including less information, for example on reconciliation (absent in PIC/S).

## Comprehensive clause-by-clause comparison

The following table provides a detailed summary of the differences between the EU and PIC/S codes for Chapter 4. Elements that are similar or the same between the two codes are not discussed in any detail within the table; refer to the separate guidance documents for further information regarding these clauses.

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| Principle | Principle | EU acknowledges that documentation may exist in a variety of forms – paper-based, electronic and photographic – PIC/S covers this requirement in Clause 4.9. All document forms (specified by each code) must be adequately controlled and defined by the documentation system of the QMS, including demonstration of that control with records and evaluation of observations.<br><br>EU classifies documentation used to manage and record GMP compliance into two types, instructions or records/reports, with GDP applied with respect to the type of document. Absent in PIC/S.<br><br>Both EU and PIC/S detail the requirements for specific documents in the General section (below). |
| NA | Required GMP doc. by type | EU details the different document types as part of the chapter preamble before individual clauses; PIC/S details this in Clause 4.1. Documents specified include:<br>• Specifications PIC/S & EU<br>• Manufacturing formulae, processing and packaging instructions, testing instructions PIC/S & EU<br>• Procedures PIC/S & EU<br>• Protocols EU<br>• Technical Agreements EU<br>• Records PIC/S & EU<br>• Certificate of Analysis (CoA) EU<br>• Reports EU |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| General<br>4.1 | | Both codes require specifications, manufacturing formulae/processing and packaging instructions, procedures and records form part of the QMS.<br>EU states that manufacturing formulae, processing, packaging and testing instructions must include equipment and computerised systems to be used and specify sampling and testing instructions (absent in PIC/S).<br>In process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria (absent in PIC/S).<br>Protocols, technical agreements, CoA and reports new to EU (absent in PIC/S).<br>EU records are required to demonstrate compliance with instructions (inferred in PIC/S). Where raw data is used to base quality decisions, it must be defined as raw data (absent in PIC/S). |
| NA | 4.1 | EU states (absent in PIC/S):<br>All document types must be defined and adhered to, across all media types. Complex systems must be understood, well documented, validated and adequate controls in place.<br>Documents may exist in hybrid forms (electronic and/or paper-based) – relationships, control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogeneous systems.<br>Appropriate controls for both electronic documents such as templates, forms and master documents, and integrity of records throughout the retention period, are required. |
| 4.2 | 4.2 | Both codes indicate that documents must comply with the manufacturing and marketing authorisation dossiers; EU also includes product specification file.<br>EU requires that the reproduction process of working documents from master documents must not introduce errors – covered by PIC/S in Clause 4.4. |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.3 | 4.3 | Both codes require documents to be approved, signed and dated by appropriate and authorised persons – EU specifies that this requirement is for documents with instructions.<br>Both codes require documents to have unambiguous content and be uniquely identifiable (PIC/S Clause 4.4).<br>EU specifies that the effective date must be defined (absent in PIC/S). |
| 4.4 | 4.4<br>(4.3)<br>(Principle) | In general, the intent of this clause is similar for both PIC/S and EU.<br>PIC/S specifies that:<br>unambiguous content applies to the title, nature and purpose, documents should be laid out in an orderly fashion, and easy to check (detail absent in EU)<br>reproduced elements must be clear and legible (covered by EU Principle).<br>EU specifies that:<br>style and language must fit the intended use of documents<br>SOPs, WIs and methods must be written in the imperative mandatory style. |
| 4.5 | 4.5 | Both codes require documents to be regularly reviewed and kept up to date. PIC/S requires a system to prevent the use of superseded documents (absent in EU). |
| 4.6 | 4.6<br>(4.7) | PIC/S and EU stipulate that documents should not be handwritten. Data entry requiring handwritten entries must have sufficient space provided for entries.<br>PIC/S requires entries to be clear, legible and in indelible handwriting – covered in EU Clause 4.7. |
| 4.7 | (4.9) | PIC/S requires alterations to an entry must be signed and dated, permitting the reading of original information and showing a reason for the change – covered in EU Clause 4.9. |
| 4.8 | 4.8<br>(4.11) | Both codes require records to be made at the time each action is taken and so that actions are traceable. Records should be retained for at least one year after the expiry date of the finished product – covered in EU Clause 4.11. |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.9 | (Principle)<br>(4.1)<br>(4.10) | Both codes indicate that data may be recorded by electronic data processing systems, photographic or other reliable means with details of the system within procedures. PIC/S requires that data must be available throughout the period of retention – covered in EU Clause 4.1 and 4.10.<br>PIC/S further specifies that:<br>Accuracy of records should be checked<br>When documents are handled with electronic data processing methods, only authorised persons are able to enter/modify data in the computer, with a record of changes and deletions<br>Access is restricted by password/other means<br>Result of entry of critical data should be independently checked<br>Electronically stored batch records must be protected by back-up transfer on magnetic tape/microfilm/paper/other means |
| NA | Retention<br>4.10 | EU requires clear definition of which records is related to each manufacturing activity and where the record is located (absent in PIC/S).<br>Secure controls are required ensuring record integrity throughout the retention period (PIC/S 4.9) and validated where appropriate (absent in PIC/S). |
| | 4.11 | EU specifies batch documentation retention:<br>Must be kept for one year after expiry of the batch to which it relates (PIC/S Clause 4.8), or at least five years after certification of the batch by the Qualified Person whichever is longer (absent in PIC/S).<br>Investigational medicinal products batch documents must be retained for five years after completion/formal discontinuation of the last clinical trial in which the batch was used (absent in PIC/S).<br>Other document retention requirements may be described in legislation in relation to specific types of products (absent in PIC/S). |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| NA | 4.12 | EU specifies other documentation retention (absent in PIC/S):<br>Depends on the business activity the documentation supports<br>Critical documentation which supports information in the marketing authorisation (e.g. raw data relating to validation or stability) should be retained for while the authorisation is in force<br>Documentation may be retired when superseded by a full set of new data, with documented justification for superseding and considering impacts to batch documents (e.g. Process validation raw data). |
| Documents required<br>4.10 | Specifications<br>4.13 | *Specifications* - Both codes require appropriately authorised and dated specifications for starting and packaging materials and finished products. PIC/S further states specifications should be available for intermediate or bulk products (intermediate requirement absent in EU). |
| 4.11 | 4.14 | *Specifications for starting and packaging materials* – Content of this clause is essentially the same between both codes. |
| 4.12 | 4.15 | *Specifications for intermediate and bulk products* –<br>Specifications for intermediate or bulk products are required:<br>if they are purchased or dispatched (both codes)<br>for critical steps (EU only)<br>if data obtained from intermediate products are used for the evaluation of the finished product (PIC/S only) |
| 4.13 | 4.16 | *Specifications for finished products* – Content of this clause is essentially the same between both codes. |
| Manufacturing formula & processing instructions | | Both codes require authorisation for each product and batch size. PIC/S indicates these may be combined in one document. |
| 4.14 | 4.17 | Manufacturing formula requirements are essentially the same between both codes. |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.15 | 4.18 | Processing instruction requirements are essentially the same between both codes except EU stipulates they must include checks that equipment and work stations are clear of previous products, documents or materials not required for the planned process and that equipment is clean and suitable for use (covered in PIC/S Clause 4.17) |
| Packaging instructions | | Content is essentially the same between both codes except EU stipulates packaging instructions must include checks that equipment and work stations are clear of previous products, documents or materials not required for the planned packing operations (line clearance) and that equipment is clean and suitable for use (covered in PIC/S Clause 4.18) |
| 4.16 | 4.19 | |
| Batch processing records | | The content of both codes is essentially the same except PIC/S requires:<br>The method of preparing batch processing records must avoid transcription errors (absent in EU)<br>Checks that equipment and work stations are clear of previous products, documents or materials not required for the planned process operations and that equipment is clean and suitable for use (covered in EU Clause 4.18)<br>Information should be recorded at the time each action is taken and the completed record signed and dated in agreement with the person responsible for the processing operations (covered in EU Clause 4.8)<br>EU notes that where a validated process is continuously monitored and controlled then automatically generated reports may be limited to compliance summaries and exception/OOS data reports (absent in PIC/S). |
| 4.17 | 4.20<br>(4.18)<br>(4.8) | |
| Batch packaging records | | |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.18 | 4.21<br>(4.8)<br>(4.19) | The content of both codes is essentially the same except PIC/S requires:<br>The method of preparing batch packaging records must avoid transcription errors (absent in EU)<br>Records must carry the batch number and the quantity of bulk product to be packed, and the batch number and the planned quantity of finished product that will be obtained (absent in EU)<br>Checks on equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations and that equipment is clean and suitable for use (covered in EU Clause 4.19)<br>Information should be recorded at the time each action is taken and the completed record signed and dated in agreement with the person responsible for the processing operations (covered in EU Clause 4.8)<br>EU states that where there are robust electronic controls in place during packaging for reconciliation there may be justification to not include quantities, reference number/identification of printed packaging material and bulk product issued/used/destroyed/returned to stock, and quantities of obtained product (absent in PIC/S). |
| Procedures and records | | *Receipt* – Both codes require written procedures and records for the receipt of each delivery of starting material, primary and printed packaging materials.<br>EU specifies that:<br>starting material includes bulk, intermediate or finished product (absent in PIC/S)<br>secondary material is included (absent in PIC/S) |
| 4.19 | 4.22 | |
| 4.20 | 4.23 | The content of this clause is essentially the same in both codes. PIC/S clarifies that records of receipt should include relevant comments such as the state of the containers. |
| 4.21 | 4.24 | Both codes require written procedures for internal labeling, quarantine, and storage of starting materials, packing materials and other materials. |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.22 | 4.25 | *Sampling* – The content of this clause is essentially the same in both codes except PIC/S requires written procedures for sampling to include the person(s) authorised to take samples (absent in EU). |
| 4.23 | 4.26 | *Testing* – Both codes require written procedures for testing materials and products at different stages of manufacture, describing methods and equipment, and tests performed are recorded. |
| 4.24 | 4.27 | *Other* – The content of this clause is essentially the same in both codes, requiring written release and rejection procedures for materials and products, and the release (PIC/S)/certification (EU) for sale by the authorised/qualified person.<br>EU stipulates that records must be available to the qualified person and a system in place to indicate special observations and any changes to critical data (absent in PIC/S). |
| 4.25 | 4.28 | Both codes require records to be maintained for the distribution of each batch of product in order to facilitate recall. |
| 4.26 | 4.29 | The intent of ensuring written procedures for other processes is essentially the same in both codes. However, EU includes:<br>all document and record types specified in EU preamble for GMP document types (policies, protocols and reports not stipulated by PIC/S)<br>additional examples such as process/equipment/system qualification, technology transfer, signature lists, training in GMP and technical matters, verification of training effectiveness, change control, investigations into deviations and non-conformances, internal quality/GMP compliance audits, summaries of records and supplier audits (absent in PIC/S) |
| 4.27 | 4.30 | Both codes require clear operating procedures for major items of manufacturing and test equipment. |
| 4.28 | 4.31 | |

| PIC/S Clause | EU Clause | Summary differences between PIC/S and EU GMP codes for Chapter 4. Documentation |
|---|---|---|
| 4.29 | | Both codes require logbooks to be kept for major/critical equipment, kept in chronological order, and include validation (absent in EU), use of an area (absent in PIC/S), calibrations, maintenance, cleaning or repair and the date/identity of operators.<br>EU stipulates logbooks are required for equipment for analytical testing, production, areas where product is processed (absent in PIC/S). |
| NA | 4.32 | EU requires an inventory of documents within the Quality Management System to be maintained (absent in PIC/S). |

## Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net

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