Overview

**PIC/S Version 10, 1st January 2013**
- Referenced as “v9” and “v10”

**EU changes effective 31st January 2013**

**Other upcoming GMP changes in the EU**
PIC/S membership
43 agencies

Current applicants
- Japan
- South Korea
- Philippines
- Brazil
- Iran
- Thailand
- UK (veterinary)

Showing interest
- Hong Kong (pre-accession)
- Nigeria (pre-accession)
- Armenia (pre-accession)
- Uganda (pre-accession)
- Mexico (pre-accession)
- PR of China
- Saudi Arabia
- Croatia
- Bulgaria
- Turkey
- Russia
- Hungary (vet)
PIC/S and EU guidelines GMP for Medicinal products

Differences

<table>
<thead>
<tr>
<th>EU</th>
<th>PIC/S</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualified person</td>
<td>Authorised Person</td>
<td>CFR</td>
</tr>
<tr>
<td>Members states</td>
<td>Participating authorities</td>
<td>Guidance documents</td>
</tr>
</tbody>
</table>

WHO GMP closer aligned with EU!

ICH
- Q7, Q8, Q9, Q10, Q11

Pharmacopeia
- USP, BP, EP
# GMP Requirements of Different Countries in this region

<table>
<thead>
<tr>
<th>Country</th>
<th>GMP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia &amp; NZ (ANZTPA)</td>
<td>PIC/S</td>
<td>Oldest version (PE009-8)</td>
</tr>
<tr>
<td>ASEAN countries</td>
<td>PIC/S</td>
<td>Old version (PE009-9)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>PIC/S</td>
<td>Old version (PE009-9)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>WHO</td>
<td>Will be PIC/S members in 2015</td>
</tr>
<tr>
<td>South Korea</td>
<td>KGMP</td>
<td>Presently filling the gaps to be equivalent to PIC/S</td>
</tr>
<tr>
<td>South Africa</td>
<td>PIC/S</td>
<td>Current version (PE009-10)</td>
</tr>
<tr>
<td>China</td>
<td>China GMP</td>
<td>Based on EU &amp; WHO GMPs (China 2010 GMPs)</td>
</tr>
</tbody>
</table>

2. Contains revised Annex 3 on “Manufacture of Radiopharmaceuticals”.

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# What has changed?

<table>
<thead>
<tr>
<th>PIC/S GMP Guide (Sept’09) v9</th>
<th>PIC/S GMP Guide (Jan’13) v10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part I</strong></td>
<td><strong>Part I</strong></td>
</tr>
<tr>
<td>Basic Requirements for Med. Products</td>
<td>Basic Requirements for Med. Products</td>
</tr>
<tr>
<td>Chapter 4: Documentation</td>
<td></td>
</tr>
<tr>
<td><strong>Part II</strong></td>
<td><strong>Part II</strong></td>
</tr>
<tr>
<td>Basic Requirements for APIs</td>
<td>Basic Requirements for APIs</td>
</tr>
<tr>
<td><strong>No Part III</strong></td>
<td><strong>No Part III</strong></td>
</tr>
<tr>
<td><strong>Annexes</strong></td>
<td><strong>Annexes</strong></td>
</tr>
<tr>
<td>1 – 20</td>
<td>1 – 20</td>
</tr>
<tr>
<td><strong>Annex 6: Man. of medicinal gases</strong></td>
<td><strong>Annex 6: Man. of medicinal gases</strong></td>
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<tr>
<td><strong>Annex 7: Man. of herbal medicinal products</strong></td>
<td><strong>Annex 7: Man. of herbal medicinal products</strong></td>
</tr>
<tr>
<td><strong>Annex 13: Man. of investigational medicinal products</strong></td>
<td><strong>Annex 13: Man. of investigational medicinal products</strong></td>
</tr>
</tbody>
</table>
## Version “v10” Chapter 4

<table>
<thead>
<tr>
<th>Code of GMP</th>
<th>Current Version</th>
<th>Previous Version</th>
<th>Chapter 4 Differences</th>
</tr>
</thead>
</table>
| PIC/S       | PE009-10        | PE009-9          | - Includes all forms of document media  
- Fully defined docs within the QMS  
- Diff. types of docs & their requirements  
- Retention periods  
- Line clearance  
- Real-time testing  
- Activities of the authorised person  
- More detailed list of processes requiring SOPs  
- Logbooks |
Chapter 4 - Key differences

- Holistic compliance of the QMS
  - v9 - stronger emphasis on holistic compliance
  - v10 - “... establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products.”
Key differences (continued)

- Types of documents
  - v10 – specifies additional systems that must have procedures and/or records, eg:
    - Technology transfer
    - Training in GMP
    - Verification of training effectiveness
  - v10 – specifies document inventory
  - All document types specified must be part of the QMS - defined and formally managed
  - Hybrid documents: appropriate control and maintaining the integrity of the data over retention time
<table>
<thead>
<tr>
<th>\textbf{“v10” document types}</th>
<th>\textbf{“v9” document types}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instructions (directions or requirements)</strong></td>
<td>Specifications</td>
</tr>
<tr>
<td>Specifications</td>
<td>Manufacturing formula</td>
</tr>
<tr>
<td>Manufacturing formulae, processing, packaging and testing instructions</td>
<td>Processing &amp; packaging instructions</td>
</tr>
<tr>
<td>Procedures (SOPs, Work Instructions, Methods)</td>
<td>Procedures</td>
</tr>
<tr>
<td>Protocols</td>
<td>Records</td>
</tr>
<tr>
<td>Technical agreements</td>
<td></td>
</tr>
<tr>
<td><strong>Records and reports</strong></td>
<td></td>
</tr>
<tr>
<td>Records</td>
<td></td>
</tr>
<tr>
<td>Certificates of Analysis</td>
<td></td>
</tr>
<tr>
<td>Reports</td>
<td></td>
</tr>
<tr>
<td>Site Master File</td>
<td></td>
</tr>
</tbody>
</table>
### Key differences (continued)

**Retention period**

<table>
<thead>
<tr>
<th>&quot;V10&quot; document type</th>
<th>Recommended duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch docs</td>
<td>1yr after the expiry date or at least 5yrs after certification (whichever is longer)</td>
</tr>
<tr>
<td>Batch docs for IMPs</td>
<td>At least 5yrs after completion/formal discontinuation of the last clinical trial in which the batch was used</td>
</tr>
<tr>
<td>Critical docs supporting Marketing Authorisation</td>
<td>Retained as long as the authorisation is valid</td>
</tr>
</tbody>
</table>
Annex 6 Manufacture of Medicinal Gases

• Greater emphasis on:
  • Control on manufacturing
  • Compliance to marketing authorisation
  • Checks to minimise cross contamination
  • Greater control of the receiving vessel
  • Product handled by trained staff rather than experienced staff
  • Confidence in the systems used to transfer gases within a facility and in the transportation of the gases

• Manufacture of medicinal gases should comply with Part 1 of the GMP guide and relevant annexes rather than should comply with basic GMP

• Manufacture of active gas substance (Bulk gases) should comply with the requirements of Part II and relevant annexes
Annex 7: Manufacture of Herbal Medicinal products

- Greater overall control of the manufacturing process
- Reference to international Good Agricultural and Collection practices
- Manufacturer’s ensure their starting materials are:
  - Have supporting documentation and data
  - Traceability
  - Have QRM system in place to mitigate non conformance to GMP
  - Distinctive testing for detection of adulterated substances
  - Checked against appropriate reference samples
Annex 11: Computerised systems

- Revised because of increased use and complexity of computerised systems
- Greater alignment with current industry guidance GAMP 5 and Eudralex GMP Vol 4 Annex 11
- Strongly promotes risk based approach to all the activities and documentation over the full life cycle of the system
- Periodic reviews to ensure validity of the system, address any issues and appropriate assess and action improvements
- Document has been structured easier to read and providing greater detail.
Annex 13: Manufacture of Investigational medicinal products

• Overall not too much has changed

• New section on Manufacturing authorisation and the reconstitution of product
  • IMP may not have marketing authorisation
  • Not required for the reconstitution of a product

• Reinforcing both production and quality responsibilities

• Additional information on retention and reference samples, relating to quantities, storage, and control

• Interesting to note: Reference to a Qualified Person and not Authorised Person.

Mistake?
## Alignment with EU

<table>
<thead>
<tr>
<th>PIC/S GMP Guide v10</th>
<th>EU GMP Guide (31st Jan’13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part I</strong>&lt;br&gt;Basic Requirements for Med. Products&lt;br&gt;Chapter 1: Quality Management&lt;br&gt;Chapter 7: Contract Manufacture and analysis</td>
<td>Part I&lt;br&gt;Basic Requirements for Med. Products&lt;br&gt;Chapter 1: Pharmaceutical Quality System&lt;br&gt;Chapter 7: Outsourced activities</td>
</tr>
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</tr>
<tr>
<td><strong>No Part III</strong></td>
<td>Part III&lt;br&gt;Site Master File&lt;br&gt;Q9 - Quality Risk Management&lt;br&gt;Q10 - Pharmaceutical Quality Systems&lt;br&gt;MRA Batch Certificate</td>
</tr>
<tr>
<td><strong>Annexes</strong>&lt;br&gt;1 – 20</td>
<td>Annexes&lt;br&gt;1 – 19 (20 = Q9)</td>
</tr>
</tbody>
</table>
Expected Future Changes to the PIC/S & EU GMP Guides

- **Chapter 1 (Quality Management)**
  (Pharmaceutical Quality systems Q10).

- **Chapter 7 (Contract Manufacture & Analysis)**
  (Outsourced Activities)
Update adopted in the EU guidelines 31st Jan:

- Change: In line with ICH Q10 Pharmaceutical Quality System (PQS)
- More emphasis on concepts of Q10 (PQS) & lifecycle approach
- Coincides with changes to Chapter 1 (including title)
  - “Quality management” to “Pharmaceutical Quality System”
  - PQS incorporates GMP and QRM
- Senior management has ultimate responsibility
- Should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities
- Use of CAPA process for continual improvement
Coming PIC/S Changes - Chapter 7

Update adopted in the EU guidelines 31st Jan:

- Change in Title for Chapter 7 to “Outsourced activities”
- Scope wider, use of QMS and QRM principles
- Contract giver to have ultimate responsibility
- Provide updated guidance on outsourced GMP regulated activities beyond **Contract manufacturing and analysis**.
What is outsourced?

- Cleaning and sanitation contractors
- Garments: Laundry and sterilisation garments
- Packaging manufacturers
- Contractors and consultants
- HEPA filter integrity testing companies
- Engineering firms design and construction
- Pest control/management
- Art work designers
- Translators
- Calibration / maintenance personnel
- And the list goes on.
• Cross-contamination should be avoided for all products by appropriate design and operation of manufacturing facilities.

• The measures to prevent cross-contamination should be commensurate with the risks.

• Quality Risk Management principles should be used to assess and control the risks.

• Risk assessment should include among other parameters a toxicological evaluation of the products being manufactured.

EMA draft - Chapters 3 and 5 cont.

- Definitive statements

- Dedicated facilities are required for manufacturing when a medicinal product presents a risk:
  
  a) Which cannot be adequately controlled by operational and/or technical measures or

  b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

  c) Threshold values derived from the toxicological evaluation are below the levels of detection
Thank you for your time. Questions?

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