Overview

1. Growing influence of PIC/S in the Asia Pacific region
2. PIC/S hot topic
3. Australia
4. ASEAN countries
5. India
6. China
7. Hong Kong
8. Vietnam
## Summary of PIC/S Influence in Asia Pacific

<table>
<thead>
<tr>
<th>PIC/S Members (at 1 July 2015)</th>
<th>PIC/S applicants being assessed</th>
<th>Interested in joining PIC/S</th>
<th>Aiming to use the PIC/S GMP Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Philippines</td>
<td>P.R. China</td>
<td>Cambodia</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Thailand</td>
<td>Brunei</td>
<td>Laos</td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td>Bhutan</td>
<td>Myanmar</td>
</tr>
<tr>
<td>Malaysia</td>
<td></td>
<td>Vietnam</td>
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<tr>
<td>Indonesia</td>
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<tr>
<td>Taiwan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td><strong>Became member on 1 July’14</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Korea</td>
<td><strong>Became member on 1 July’14</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong</td>
<td><strong>Will become member from 1 Jan’16</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Higher Proportion of Critical & Major GMP Deficiencies found in Asia

The relative number of Critical & Major GMP deficiencies raised per inspection by MHRA in 2013 was higher in Asia than other continents where MHRA inspections were carried out.

Source: [http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con464241.pdf](http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con464241.pdf)
“Data Integrity” - a hot topic for many PIC/S Inspectorates

• Since mid-2013, data integrity has become a major focus of attention by many PIC/S Inspectorates.

• For example, over the past 2 years, 15 India manufacturers have received warning letters from US FDA because of serious data integrity breaches\(^1\). Supply of products to USA halted.

• Similar experiences by MHRA, TGA, ANMS, etc. in various parts of the world, including Asia & Europe.

• PIC/S Inspectorates share experiences on data integrity breaches.

• MHRA so concerned that they issued a "Data Integrity Definitions & Guidance for Industry" in January 2015 (updated in March 2015\(^2\)).

Sources:
\(^1\) [http://www.raps.org/Regulatory-Focus/News/2014/08/19/18980/Indias-Data-Integrity-Problems-Updated-17-June-2014/](http://www.raps.org/Regulatory-Focus/News/2014/08/19/18980/Indias-Data-Integrity-Problems-Updated-17-June-2014/)

### Examples of Data Integrity Breaches

<table>
<thead>
<tr>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;<strong>Audit trails</strong> not available or not enabled for electronic data acquisition systems” (computer system).&quot;</td>
</tr>
<tr>
<td>&quot;<strong>Time/date function</strong> for electronic data acquisition systems not disabled by the system administrator”.</td>
</tr>
<tr>
<td>&quot;<strong>Multiple users share</strong> the same user name &amp; password”.</td>
</tr>
<tr>
<td>&quot;All users can log on <strong>as administrator</strong> with privileges that include ability to modify &amp; delete data”.</td>
</tr>
<tr>
<td>&quot;<strong>Two versions of OOS</strong> used; with the 2(^{nd}) (unofficial) version showing more excursions than had been reported in the 1(^{st}) version”.</td>
</tr>
<tr>
<td>&quot;<strong>Stability failures</strong> not reported”.</td>
</tr>
<tr>
<td>&quot;Batch packaging record recorded only one machine operator for a blister packing machine, when <strong>in fact two operators</strong> were used”.</td>
</tr>
<tr>
<td>&quot;<strong>Staff training records fabricated</strong>”.</td>
</tr>
</tbody>
</table>

Data Integrity is not just IT related: example from MHRA
ISPE Data Integrity special interest group

Global Membership
- 85 active members + 5 leaders = 90
- Representatives from US, UK, Netherlands, Canada, Switzerland, Belgium, Scotland, Germany, Denmark, Australia, Italy, Austria
- 52 members are in the Pharma industry or computer systems.

Regulatory Agency Participants
- US FDA: Karen Takahashi, Johnathan Bray
- MHRA: Chris Gray, Tracy Lovatt
- Health Canada: Neil Barat, Rosalee Scarito
- TGA: considering joining

Advisory Committee Members
- Monica Cahilly
- Karen Takahashi
- Bob McDowall
- Sion Wyn
- David Selby
- Others resources when appropriate
Objectives: ISPE Data Integrity SIG

**Objective 1**
Understand the current and future regulatory expectations, guidance, and enforcement strategies.

**Objective 2**
Identify and propose appropriate data integrity control strategies for critical data and key quality attributes throughout the lifecycle by applying risk-based control strategies that focus on not only prevention, but also detection of data integrity issues. These strategies must also address the management of the data during the operational phase through the record retention phase.

**Objective 3**
Provide the tools to align data integrity requirements with their product lifecycle.

**Objective 4**
Provide a pragmatic and tangible framework for managing data integrity risks within the global and increasingly complex pharmaceutical industry.
# Regulators becoming more transparent

<table>
<thead>
<tr>
<th>Regulator</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>US FDA</td>
<td>Publish establishment inspection reports, FD483s, warning letters, enforcement reports, etc.</td>
</tr>
<tr>
<td>EudraGMP database</td>
<td>Publish manufacturer authorizations, GMP certificates, GMP inspection planning in 3\textsuperscript{rd} countries, non-compliant &amp; faulty manufacture.</td>
</tr>
<tr>
<td>Health Canada</td>
<td>Publish inspection tracker (emerging issues identified through GMP inspections).</td>
</tr>
<tr>
<td>PIC/S member authorities</td>
<td>Many PIC/S authorities publish list of licensed manufacturers on their web site.</td>
</tr>
<tr>
<td>WHO PQ</td>
<td>Publish all “WHO Public Inspection reports” (WHOPIIRs) on WHO web site.</td>
</tr>
</tbody>
</table>
EudraGMDP Database
Good Manufacturing and Distribution Practice

Version 1:
• Manufacturing Authorisations
• GMP Certificates

Version 2: GMP non-compliance

Version 3: Inspection plans in 3rd countries

Version 4: Information on "faulty Manufacture"
Wholesale Authorisations and GDP Certificates

• Limited public access phased in from 2009-2011.
• Access by MRA partners and other regulatory agencies in progress
• Developed and maintained by EMA

Opened since 1st February 2011 partially to the public, with information on compliant and non-compliant manufacturers

Search capabilities
Alert on event capabilities

Links to other Community databases e.g. EudraCT
## GMP Requirements of Various Asia Pacific Countries

(current version of PIC/S Guide to GMP is **PE 009-11**, 1 March 2014)

<table>
<thead>
<tr>
<th>Country</th>
<th>GMP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia &amp; NZ</td>
<td>PIC/S</td>
<td>Jan’09 version applies (PE 009-8)</td>
</tr>
<tr>
<td>ASEAN – PIC/S countries</td>
<td>PIC/S</td>
<td>Current version applies (PE 009-11)</td>
</tr>
<tr>
<td>ASEAN – other countries</td>
<td>ASEAN or WHO</td>
<td>Under ASEAN Sectoral MRA, are obliged to migrate to PIC/S GMP</td>
</tr>
<tr>
<td>Taiwan</td>
<td>PIC/S</td>
<td>Current version applies (PE 009-11)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>WHO</td>
<td>Current version to be apply from Oct’15</td>
</tr>
<tr>
<td>South Korea</td>
<td>KGMP</td>
<td>Have filled gaps to be equivalent to PIC/S</td>
</tr>
<tr>
<td>Japan</td>
<td>JGMP</td>
<td>Have filled gaps to be equivalent to PIC/S</td>
</tr>
<tr>
<td>China</td>
<td>China GMP</td>
<td>Based on EU, PIC/S &amp; WHO GMPs</td>
</tr>
</tbody>
</table>

1. Singapore, Malaysia, Indonesia, Philippines.
TGA Australia - Recent Developments

ANZTPA project abandoned (Australia NZ Therapeutic Products Agency) Instead, an MRA on GMP inspections to be developed.

Review of medicines regulations (announced October 2014). Looking at unnecessary, duplicative or ineffective regulation that could be removed or streamlined.

- Describes requirements & responsibilities of the “Authorised Person”.
- Includes a requirement for medicines entering Australia to be “released for supply” in Australia (already applies in NZ).

Guidance document on “Licensing/certification inspections” (Apr’13)
- Provides detailed description of TGA’s inspection and licencing procedures for medicine manufacturers, including examples of GMP deficiencies (critical, major, minor).
- TGA now uses the term “inspection” rather than “audit”.

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Medicines cannot be imported into Australia until evidence of GMP compliance is provided and a “GMP Clearance” is issued by the TGA.

Three types of evidence accepted:

1. A GMP inspection by an MRA regulator (EU, Canada, Singapore) in their own country. Always accepted.

2. A GMP inspection by:
   - an MRA regulator in third countries, or
   - an MOU or PIC/S regulator in their own or third countries, e.g. US-FDA & NZ. These are formal arrangements, but with option not to accept. Additional information may be required depending on product risk.

3. TGA inspection (full cost recovery, including inspection fee and travel costs).
TGA, Australia
Reform of “GMP Clearance” process

- Significant increase in GMP clearances since 2010:
  - 2500 GMP clearances in 2010/11.
  - 4000 GMP clearances in 2014/15.
- Has resulted in TGA not meeting target timelines.
- Review being undertaken to streamline GMP clearance process.

ASEAN: Association of Southeast Asian Nations

- Founded in 1967.
- Comprises 10 countries of South East Asia.
- Combined population of 650 million people.
- Will become 5th largest world economy by 2020.
ASEAN Harmonization

- ASEAN is aiming to harmonize regulations prior to the establishment of an **ASEAN Economic Community (AEC)** by the end of 2015.

- An ASEAN Sectoral MRA on GMP inspection was signed in 2009.
  - Obliges each member country to have a PIC/S-equivalent GMP inspection framework.
  - Obliges non-PIC/S countries to migrate towards adopting PIC/S GMP Guide.
  - Covers medicinal products only *(the MRA excludes APIs, biologicals & herbals).*

- ASEAN is collaborating with PIC/S, ISPE & other parties to assist with training & developing equivalency.

- Only Singapore, Malaysia & Indonesia are PIC/S members.

- Those countries listed as **“ASEAN accepted inspection services”**:  
  ➢ Singapore, Malaysia & Indonesia (through their PIC/S membership), &  
  ➢ Thailand (assessed by ASEAN Panel of Experts in September 2014).

- Vietnam soon to be assessed as an “ASEAN accepted inspection service”.
Benefits of ASEAN MRA on GMP

- Avoids duplication of GMP inspections within ASEAN.
- Savings of time, resources & costs for regulators & industry.
- Facilitates trade in medicinal products across ASEAN.
- Quicker access to medicines by patients within ASEAN.
- Increased competitiveness of ASEAN countries. (viz-a-viz India, China & other large industrialized countries)

NB: Singapore, Malaysia, Vietnam & Brunei are parties to the proposed TPP trade agreement
Further information: “ASEAN Harmonization on GMP Inspection and Training of Inspectors”. Pharmaceutical Engineering, Jan/Feb 2013 2013: 56-62, Sia Chong Hock, Robert Tribe, Dr. Chan Lai Wah
India

- Population: 1.2 billion
- World’s largest democracy.
- 29 State governments
- Regulator is “CDSCO” (Central Drugs Standard Control Organization)
GMP Regulatory Controls - India

- GMP requirements (“Schedule M”) issued by CDSCO (Central Drugs Standard Control Organization, India).
  - “Schedule M” modelled on WHO GMP, but not equivalent to WHO or PIC/S GMPs.

- Responsibility for GMP is divided between Central and State governments (some joint inspections of “high risk drugs” undertaken):

<table>
<thead>
<tr>
<th>Central government (CDSCO)</th>
<th>State governments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laying down standards for drugs.</td>
<td>Inspect &amp; license drug manufacturers.</td>
</tr>
<tr>
<td>Issue market authorization new drugs.</td>
<td>Pre &amp; post licensing inspections.</td>
</tr>
<tr>
<td>Regulate imported drugs, including some overseas inspections.</td>
<td>Inspect &amp; license drug testing laboratories.</td>
</tr>
<tr>
<td>License manufacturers of “high risk drugs” such as LVPs, vaccines, sera.</td>
<td>Coordinate drug recalls.</td>
</tr>
<tr>
<td>Testing of drugs by Central Drugs Laboratories</td>
<td>Investigation &amp; prosecution of breaches of legal provisions.</td>
</tr>
</tbody>
</table>
Issues Specific to India

- 40% of OTC & generic prescription medicines consumed in USA come from India. About 550 sites approved by US FDA.
- US FDA investigators are currently blitzing Indian drug plants.
- Data integrity fraud a major problem in India.
- Half of all US FDA warning letters in 2013 were for Indian drug manufacturers supplying USA.
- WHO has estimated that 1 in 5 drugs made in India are counterfeit or fake.
- Convictions of drug counterfeiters in India are extremely rare.
- Government is resisting industry requests to join PIC/S.

Sources:
China

- Population: 1.35 billion
- 22 Provinces
- 5 autonomous regions
- Regulator is “CFDA” (China Food & Drug Administration)
China – Getting Serious

• Director of SFDA (Zheng Xiaoyu) was EXECUTED in July 2007.
  – Accepted bribes in exchange for drug production licences.
  – Resulted in patient deaths from fake/substandard medicines.
• Powerful message to regulators & companies that corruption will not be tolerated.
• On the day after the execution:
  – A stricter approval process for new drugs introduced.
  – Drug approvals made by special panel (not one person).
  – Greater transparency (companies have access to approvals).
• Gradual introduction of other reforms to bring China’s regulatory controls closer to international levels.
• Nationwide crackdowns on sale of fake & counterfeited medicines.
New China GMPs

• China Good Manufacturing Practice (2010 version)
  – Came into operation in March 2011.
  – Is a combination of PIC/S and WHO requirements.
  – Sterile & biological products must have complied by 31.12.13.
    – Other products must comply by 31.12.15.

• Five Annexes:
  – **Annex 1:** Sterile Medicinal Products
  – **Annex 2:** Active Substances Used as Starting Materials
  – **Annex 3:** Biological Products
  – **Annex 4:** Blood Products
  – **Annex 5:** Chinese Traditional Medicines

• The new China GMP & Annexes not yet equivalent to PIC/S, but currently work being done (draft Annexes) to bring closer to PIC/S.
# Pharmaceutical Manufacturers in China Compliance Status  
*(as at November 2014)*

<table>
<thead>
<tr>
<th>Product type</th>
<th>Number of manufacturers</th>
<th>Number with GMP certification</th>
<th>% with GMP certification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile drug product manufacturers</td>
<td>1319</td>
<td>917</td>
<td>70%</td>
</tr>
<tr>
<td>Non-sterile drug product manufacturer</td>
<td>3839</td>
<td>2240</td>
<td>60%</td>
</tr>
</tbody>
</table>

**NB:** Does not include “export only” manufacturers

Recent GMP Issues in China (1)

New GMP Annexes (1 July 2014)
- Prepared slices of Chinese Crude Drugs
- Medicinal Gases
- Sampling

Draft GMP Annexes.
- Qualification and Validation
- Computerized systems
- Risk Assessment Management

Proposal on un-announced inspections (for public comment).
- To investigate complaints, product quality risks, spot checks, etc.
- Outside experts & journalists can be invited to join inspection team.
Recent GMP Issues in China (2)

Aim of CFDA is to apply for PIC/S membership, starting with an application for a pre-accession audit (not known when this will be).

Decentralization of GMP inspections.
- After 2015, all GMP inspections within China to be conducted by provincial FDA inspectors.

GMP controls over APIs recently strengthened.
- GMP compliant API manufacturers issued with a drug licence.
- However, still limited controls over brokers.

CFDA currently trialling an overseas inspection program.
- Guidelines issued in August 2012 about this trial.
- Requires key documents, including SMF (in PIC/S format).
Recent Contamination Scares in China

- **Heparin (2008)**
  - >230 deaths; >900 adverse reactions
  - Heparin injection contaminated with the synthetic chemical “OCSC” (over sulphated chondroitin sulphate)
  - Intentional adulteration by some Chinese factories to save Heparin (2008)

- **Melamine (2008)**
  - 6 deaths; 54,000 babies hospitalised
  - Synthetic melamine added to milk powder to increase nitrogen content
  - Sanlu Milk Products, China (owned by Fonterra, NZ)
  - Helen Clark, then NZ Prime Minister pressed Beijing officials to total recall
  - Top two company officials executed in late 2009 as punishment.

- **Chromium in hard shell capsules (2012)**
  - No deaths
  - Empty hard shell gelatin capsules contaminated with high levels of chromium.
Chromium Contamination (empty hard shell gelatin capsules)

Companies pull tainted medicines

DOCTORS WARN AGAINST OPENING CAPSULES

By Chengu Xun

Three pharmaceutical companies have recalled their chromium-contaminated drug capsules after authorities suspended sales of 13 types of problematic medicines. Jingtian Yuesen Pharmaceuticals in Northeast China’s Jilin province said the company decided to recall all tainted products made since 2010.

“Pharmaceutical producers do not possess the capability to examine capsules, so we just simply check the quality report provided by capsule suppliers and then let them go,” an anonymous official with the company’s product quality department was quoted as saying by Xinhua News Agency.

But the company and the producer of the problematic capsules are two different entities. The announcement was made by the company itself.

China Daily, Beijing, 18.4.12

Global Times, Beijing, 18.4.12

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Chromium Contamination (empty hard shell gelatin capsules)

Involved high levels of chromium contamination in empty hard shell gelatin capsules.

**Cause:**

- A gelatin factory in Hebei Province in China used leather scraps (including discarded shoes) to make gelatin.
- This industrial-grade gelatin sold to capsule manufacturers throughout China (*medical-grade gelatin is made from animal bones*).
- Many drug recalls in China.
- The Managing Director of the factory detained by police as he was suspected of setting fire to his factory to eliminate evidence.
- Gelatin & gelatin capsules added to SFDA list of 28 high risk excipients.

**Messages:**

- Audit your suppliers of empty gelatin capsules (if imported from China).
- Carry out QC testing on empty gelatin capsules & include a test for chromium.
Hong Kong
(Drug Office, Department of Health, Hong Kong)

- Will become a member of PIC/S from 1 January 2016.
  - Herbal medicines excluded.
- GMP requirement is currently the WHO GMPs.
- From 1 October 2015, PIC/S GMPs will be mandated.
- Unique Hong Kong requirements:
  - Hong Kong Guide to GMP for secondary packaging of pharmaceuticals\(^1\) (Guidance document).
  - Guidelines on Application of Registration as an Authorised Person\(^2\) (Guidance document).
  - Guidance Notes for industry: CSV, PV, PQR, QRM, Micro labs, etc.

Vietnam
(Drug Administration of Vietnam – DAV)

• GMP requirement in Vietnam is the current WHO GMPs, i.e.
  ➢ WHO TRS 986 of 2014 (non-sterile medicines), and
  ➢ WHO TRS 961 of 2011 (sterile medicines).
• DAV is currently preparing to apply for PIC/S membership.
• DAV expected to adopt PIC/S GMPs by 2019 (after a 3 year transition).
• Unique DAV requirement for primary packaging materials:
  ➢ “GMP certification” required in new drug submissions for the manufacturers of
    primary packaging materials used in each pharmaceutical product. This
    certification can be:
    - GMP certificate of packaging manufacturer from health authority of country
      where packaging manufacturer is located, or
    - ISO 15378 certification (Primary Packing Materials for Medicinal Products)
      of packaging manufacturer.
Thank you for your time.

Questions?

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