Regulatory Need: Harmonized PIC/S GMP, Its Overview and Comparison with WHO GMP

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Abstract
Currently, it is necessary to increase harmonization efforts in setting regulatory requirements, inspecting and evaluating GMP compliance, licensing manufacturing sites, recalling defective batches and increasing the exchange of information due to the increased globalization regulatory authorities. PIC/S offers an attractive and stable platform to respond to such challenges of the globalization. PIC/S actively encourage networking by organizing a “PIC/S GMP Forum” which allow non-member authorities, professional and other organizations to meet informally with the PIC/S Committee. PIC/s has established harmonized guide on GMP requirements for inspectorate and industry. There is the complementarity co-operation between the PIC/S and other organization. PIC/S participating authority co-operates actively and avoids the duplication of his member’s efforts. Till date, 46 countries are the member of the PIC/S and 10 countries are under Accession and Pre-Accession Procedure. PIC/S provide the sharing of the inspection report between the member authorities which allow them to prove their GMP facility equivalent to PIC/S standard and resulting into the reduction of the number of inspection and duplication of the inspection. Joining to PIC/S will endorse the Indian pharmaceutical companies to be reliable exporters of quality medicines globally. While for Indian Pharma Companies to meet the PIC/S requirement would not be like cakewalk especially for MSME Pharma segment that needs to upgrade their GMP facilities. Thus it will be challenging for stake holders to join PIC/S but simultaneously there will be bigger hurdles of not joining the PIC/S. While approaching to PIC/S, a careful examination is needed by India during export as maintaining high quality standards for export markets. PIC/S is bringing a great revolution in the GMP standards to establish the high quality in the drug product and thus INDIA should become the member of PIC/S to raise its GMP standards as it is recognized as ‘power house’ of pharmaceutical manufacturing.

Keywords: PIC/s; WHO GMP; PIC/s GMP; Harmonized GMP; Regulatory need

Abbreviations
WHO: World Health Organization; EMEA: European Medicines Evaluation Agency; EU: European Union; EFTA: European Free Trade Association; TGA: Therapeutic Goods Administration; FDA: Food and Drug Administration; PIC: Pharmaceutical Inspection Convention; PIC/S: Pharmaceutical Inspection Cooperation/Scheme; GMP: Good Manufacturing Practice; MSME: Ministry of Micro Small and Medium Enterprise; IMID: International Medicinal Inspectorate Database; CEP: Certificate of Suitability; API: Active Pharmaceutical Ingredients

Introduction
Pharmaceutical Inspection Co-operation Scheme was established on the 2nd November 1950 as it is extension of the Pharmaceutical Inspection Convention which was founded in 1970. As PIC was founded by the European Free Trade Association (EFTA) under the title of "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products", with aim of removal of non-tariff barrier in trade of pharmaceutical in Europe through mutual recognition of inspection report and certification

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on good manufacturing Practice. There was the legal treaty between the 10 member countries initially, i.e., Austria, Denmark, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden, Switzerland and United Kingdom. Later on other countries Hungary, Ireland, Romania, Germany, Italy, Belgium, France and Australia became the member of the PIC as it was expanded subsequently [1-8].

The goals [1] of the PIC was:
- Mutual recognition of inspections
- Harmonization of GMP requirements
- Uniform inspection systems
- Training of inspectors
- Exchange of information
- Mutual confidence

In early 1990s, it was realized that as per EU law only European Commission was authorized to sign agreements with other countries. Thus expansion of PIC cannot be possible unless European Commission became a member results into incompatibility. If PIC was to survive and expand, a way had to be found to overcome this legal impasse while retaining the main functions of PIC. Consequently PIC/S was established and both PIC and PIC/S operates parallel under the same logo and abbreviation. While the major difference between PIC and PIC/S has been depicted in Table 1 [1].

PIC/S is an informal cooperative arrangement between regulatory authorities in the field of Good Manufacturing Practice of Medicinal products for human or veterinary use. PIC/S also provides a comparable GMP inspection as it is open to authorities. As the scheme is an arrangement between authorities, it is very flexible, dynamic and proactive. PIC/S provides Good Manufacturing Practice (GMP) inspection reports and GMP certificates to be exchanged, but unlike PIC there is no legal obligation that member authorities must accept such reports or certificates [1].

The PIC/S goal is:

To lead the international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products [1].

The main functions of PIC/S are:
- To ensure that all Members comply with PIC/S standards (assessment of new applicants and reassessment of older inspectorates).
- To provide a forum for networking and confidence building amongst inspectors [1,7].

The success of the PIC Scheme is based on the common sharing of the unwritten concepts or principle like [5]:
- Technical expert’s Organization: It is purely technical organization in GMP regulatory field without getting involved in any political or discrimination issues. It is a major think-tank where new ideas related to GMP are debated by experts.
- Based on consensus and mutual trust: Every member has the equal rights and obligations are the base of the consensus in the PIC/S. While without isolating any member PIC/S always found a way forward and never let any to feel alone against the vast majority. Voluntary co-operation and assessment of the members for equivalence before membership are the major concept to establish the mutual trust.
- Driven by members: The organization is driven by its member’s, i.e., participated regulatory authorities and secretariat who contribute to either PIC/S events or PIC/S functioning.
- Cemented by strong professional and personal links: A forum established for the brain storming, discussion on new ideas and information sharing with help of networking, PIC/S informal character and the strong personal link between individual member and inspectorate is the strength of PIC/S.

To PIC/S growing membership, a new sub-committee structure [8] has been developed as shown in Figure 1 in order to:
- Favour to the participating authorities for participation.
- Establish a more participative and efficient organization of PIC/S, where each sub-committee will be responsible for its respective core areas and will take the lead in developing policies.

**Membership procedure and assessment**

A detailed assessment of the regulatory authority is carried out to determine the equivalence of necessary arrangements and competency required for inspection system that of the current members before involving the regulatory authority in PIC/S. For the existing members also reassessment is also carried out for equivalence on regular basis. As it ensure that both new applicant and older member have to fulfill the same requirements. The relation with the organization is reviewed on the basis of (i) non- discrimination and equal treatment and (ii) non-duplication with member authorities. An examination of the authority’s inspection and licensing system, quality system, legislative requirement, inspector training etc. and to observe inspectors carrying out routine GMP inspection on visit done by PIC/S delegation are included in the assessment procedure as shown on Figure 2 [1,5,8].

While Membership procedure is divide into two parts:

**Pre-accession procedure [1,8]:** A new time period offers a softer approach and adjustment period by this procedure to the new applicant who have notable difference or may not familiar to the PIC/S standard. The time period for this procedure is 3 to 6 years in which the assessment and gap analysis of the applicant authority to PIC/S is carried out as well as during this procedure auditor appointed by the committee might take visit to the site. If inspectorate come under the specified condition as below, than only pre-accession has to be done:

| PIC          | PIC/S          |
|--------------|----------------|
| Convention   | Scheme         |
| Between Countries | Between Authorities |
| A formal treaty | Informal Arrangement |
| Has legal status | Has no legal status |
| Focus only on inspection | Focus on inspection, training & developing guidelines |
| Mutual Recognition of inspection | Exchange of information |

**Table 1:** Comparison between PIC and PIC/S.
- The PIC/S GMP Guide does not apply to inspectorate,
- Inspectorate has not regularly participated in PIC/S training activities,
- Inspectorate is unsure whether it meets PIC/S requirements,
- Inspectorate has not yet introduced a QS similar along the lines of the PIC/S recommendation (PI 002),
- Inspectorate has requested to go through the pre-accession procedure.

**Accession procedure [1,8]:** It is time consuming process which provide some time to the inspectorate for completing the application and provide all necessary translation of the supporting documents. During this time inspectorate may have to take necessary measures to meet the PIC/S requirement and allow sufficient time for national industry to comply with PIC/S GMP guide (Figure 3).

**PIC/S GMP guide**

To develop GMP guidance document or new amended annexes to PIC/S GMP Guide for Medicinal product the PIC/S working group is formed at the end of the annual PIC/S seminar. PIC/S guide is divided into two parts: Parts-I covers GMP principles for the manufacture of medicinal product and Part-II covers the GMP for active substance used as the starting materials. While it also contains Annexes, which provide the details on the specific area of activity. PIC/S work closely and co-operatively with European Medicines Evaluation Agency (EMEA) and EU to minimize duplication of effort in development of GMP guidance Document and GMP Guide through its working group.

![Figure 1: PIC/S new structure.](image1.png)

![Figure 2: Steps of accession procedure.](image2.png)
The benefits [1,7] of PIC/S membership for regulatory authorities are fairly obvious, and include the following:

- The PIC/S GMP Guide uses the term ‘authorized person’ (rather than the term ‘Qualified Person’ in the EC GMP Guide).
- References to EU Directives have been removed from the PIC/S GMP Guide.

GMP Guide.

The PIC/S GMP guide is derived from the WHO GMP guide and developed in order to comply with the stringent manufacturing and health requirements in the member countries. WHO GMP has detailed guidelines compared to the PIC/S GMP [3,6] shown in Table 2.

Benefit of PIC/S Membership

The benefits [1,7] of PIC/S membership for regulatory authorities are fairly obvious, and include the following:

Table 2: Comparison of PIC/S GMP and WHO GMP.

| Topic                        | PIC/S GMP Guide                                                                 | WHO GMP Guide                                                                 |
|------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Quality Management           | • Chapter 1 in guide                                                          | TRS 961 Annex-3                                                              |
|                              | o It is divided into:                                                         | • Chapter-1: Quality Assurance                                               |
|                              | o Quality assurance                                                          | • Chapter-2: GMP for pharmaceutical products                                |
|                              | o Quality control                                                            | • Chapter-17 (Point-17.1,17.3): Good Practice in Quality control             |
|                              | o GMP for medicinal Product                                                   | • Page-103: Quality management in the medicines                               |
|                              | o Product Quality Review                                                     | industry: philosophy and essential elements                                   |
|                              | o Quality risk management                                                    |                                                                               |
| Personnel                    | • Chapter-2                                                                  | TRS 961 Annex-3                                                              |
|                              | o It is divided into:                                                         | • Chapter-9: Personnel.                                                       |
|                              | o Key Personnel                                                              | • Chapter-10: Training                                                       |
|                              | o Training                                                                   | • Chapter-11: Personal Hygiene                                               |
|                              | o Personnel Hygiene                                                          | • Chapter-3: Sanitation and Hygiene.                                         |
| Premises and Equipment       | • Chapter-3                                                                  | TRS 961, Annex 3                                                             |
|                              | o It is divided into:                                                         | • Chapter 12: Premises                                                       |
|                              | o Premises                                                                   | • Chapter 13: Equipment                                                       |
|                              | o General                                                                    | • Chapter 9 (Point 9.5): Personnel                                           |
|                              | o Production Area                                                            | • Chapter 16 (Point 16.9, 16.23, 16.24): Good practice in production         |
|                              | o Storage Areas                                                               |                                                                               |
|                              | o Quality Control Areas                                                      |                                                                               |
|                              | o Ancillary Areas                                                            |                                                                               |
|                              | • Equipment                                                                  |                                                                               |
| Documentation                | • Chapter -4                                                                 | TRS 961, Annex 3                                                             |
|                              | o It is divided into:                                                         | • Chapter-15: Documentation                                                   |
|                              | o Required GMP Documentation                                                 |                                                                               |
|                              | o General                                                                    |                                                                               |
|                              | o Production Documentation                                                   |                                                                               |
|                              | o Good Documentation Practices                                               |                                                                               |
|                              | o Retention of Documents                                                      |                                                                               |
|                              | o Specifications                                                             |                                                                               |
|                              | o Manufacturing Formula and Processing Instructions                          |                                                                               |
|                              | o Procedures and Records                                                     |                                                                               |
| Production                   | • Chapter-5                                                                  | TRS 961, Annex 3                                                             |
|                              | o It is divided into:                                                         | • Chapter 14: Materials                                                       |
|                              | o Prevention of cross-contamination in production                            | • Chapter 16: Good practices in production                                    |
|                              | o Validation                                                                 | • Chapter 5: Sanitation and hygiene.                                         |
|                              | o Starting materials                                                         | • Chapter 15 (Point 15.10): Documentation                                     |
|                              | o Processing operations - Intermediate and bulk products                     | • Chapter 4 (Point 4.4, 4.8): Qualification and validation                   |
|                              | o Packaging materials                                                        |                                                                               |
|                              | o Packaging operations                                                       |                                                                               |
|                              | o Finished products                                                          |                                                                               |
|                              | o Rejected, recovered and returned materials                                  |                                                                               |
| Quality Control              | • Chapter-6                                                                  | TRS 961, Annex 3                                                             |
|                              | o It is divided into:                                                         | • Chapter 17: Good practices in quality control                              |
|                              | o Good Quality Control Laboratory Practice                                   | • Chapter 14 (Point 14.34, 14.35, 14.39, 14.42):                           |
|                              | o Documentation                                                              | • Chapter 9 (Point 9.12): Personnel                                         |
|                              | o Sampling                                                                  | TRS 961, Annex 4                                                             |
|                              | o Testing                                                                   | • Chapter 2 (Point 2.2): Glossary and abbreviations                         |
|                              | o On-going Stability Program                                                 | TRS 961, Annex 6                                                             |
|                              |                                                                               | • Chapter 10 (Point 10.3): Personnel                                         |
|                              |                                                                               | TRS 957, Annex 2                                                             |
|                              |                                                                               | • Chapter 7 (Point 7.33): Materials management                               |
| Contract Manufacture and    | • Chapter-7                                                                  | TRS 961, Annex 3                                                             |
| Analysis                     | o It includes details of:                                                    | • Chapter 7: Contract production and analysis                                |
|                              | o Contract Giver                                                            |                                                                               |
|                              | o Contract Acceptor                                                          |                                                                               |
|                              | o Contract                                                                   |                                                                               |
| Complaint and Product        | • Chapter-8                                                                  | TRS 961, Annex 3                                                             |
| Recall                       | o It includes details of:                                                    | • Chapter 5: Complaints                                                      |
|                              | o Complaints                                                                | • Chapter 6: Product recalls                                                 |
|                              | o Recalls                                                                   |                                                                               |
Training of inspectors through participation in PIC/S Seminars and expert circles as well as in the PIC/S Joint Visits Program.

- Helps to coordinate training of inspectors
- Helps to enhance global harmonization of GMP

Conclusion

WHO-GMP standards are more stringent than PIC/S-GMP standards but PIC/S has its own benefits, e.g., it helps the membered authority by to trade the medicinal products in the other member countries by removing the barrier as they all will be following the same PIC/S GMP standards. PIC/S GMP also provide the platform to promote the uniformity in licensing decision as well as to ensure the high standards of quality assurance in the development, manufacture and control of medicinal products. The IMID will also strengthen the partnership among the IMID users by providing the information regarding the inspections of the every membered authority. If India decides to implement PIC/S standard, adequate time and financial support to Pharma companies should be provided by the government at affordable cost. As SMEs are schedule M complaint, they need to upgrade themselves by upgrading their facilities and equipment to WHO-GMP and PIC/S-GMP requirements and also require training on Quality Management System, Quality Risk Management, Product Quality Review, Stability studies and Change control.

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