Potential Areas for Improvement Of GMP Compliance Assessment

Development and utilization of Site Master File

Suggestions from JPMA

3rd India -Japan Medical Products Regulatory Symposium

Japan Pharmaceuticals Manufacturers Association
(JPMA), Quality & Technology Committee

August 27th, 2018

Tomonori Nakagawa

JPMA

Agenda

1. Establishment of Access to Innovative Medicine (ATIM)
2. Suggestions from JPMA
3. Experience of Product Application from Japan to Asian Authorities
4. Issues Related to Submitting Site Master Files (SMFs)
5. Consensus of ATIM Session in 2018

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Establishment and Accomplishment of Access To Innovative Medicine (ATIM) to People In Asia

Focus of ATIM and Next Step of the Discussion

- Innovation of new drug is the driving force to fulfil the unmet medical needs. IP, forms the foundation for innovation, and is most important to improve ATIM.
- In addition to DA & RA, APAC further discuss the possibility to set up a new EWG or project team, which covers GMP reviews.
- Regulatory environment should be improved with speeding up the evaluation/approval process in each Asian country and improve access to innovative new medicines for the patients
- PMDA Asia Training Center and training program, APEC/GRM/COE aim to improve the level of regulatory environment.

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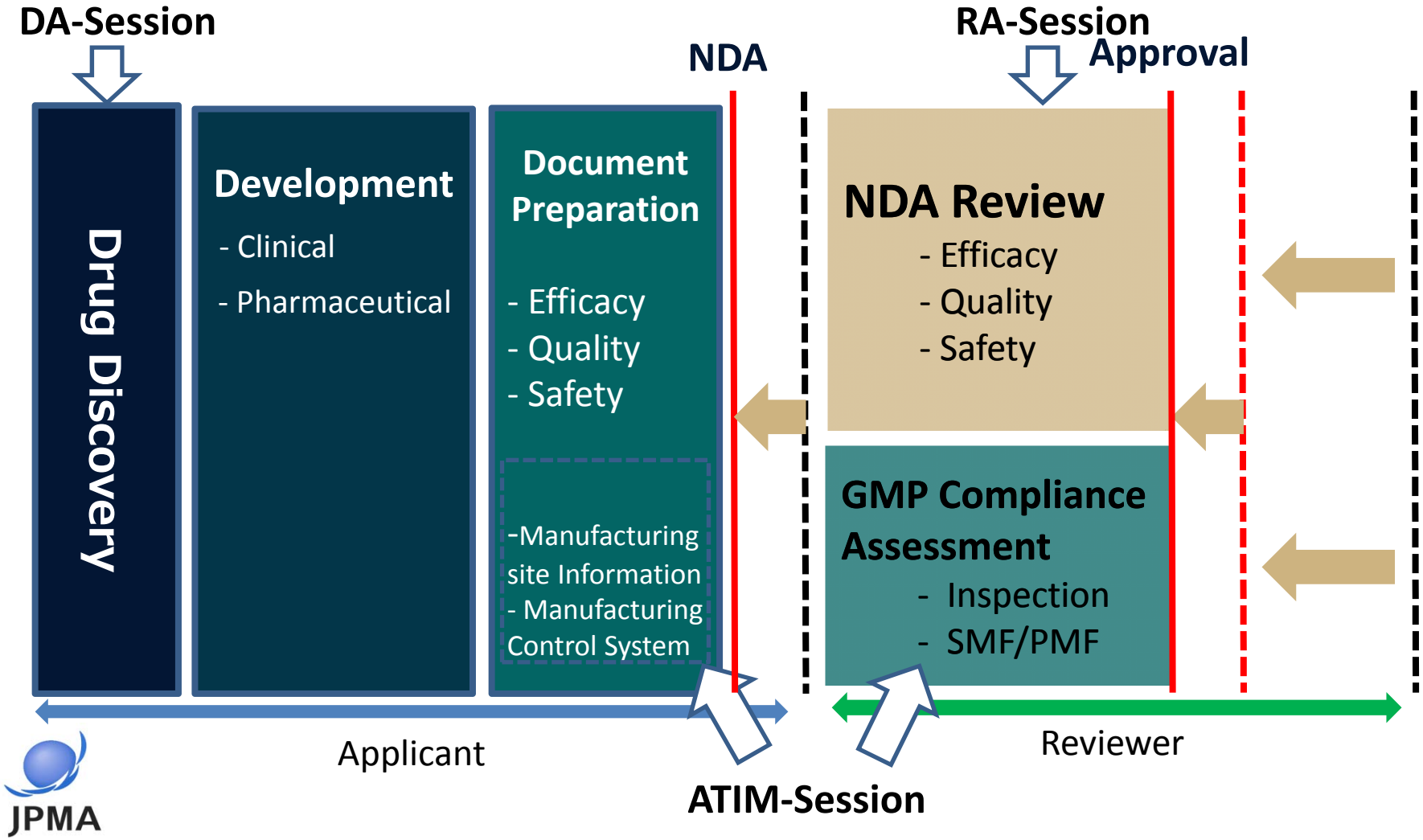
APAC's Focused areas to realize our mission "To Expedite the Launch of Innovative Medicines for the Peoples in Asia"

Efficient GMP compliance assessment will contribute to realize APAC's mission



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Suggestions from JPMA: To Promote ATIM to People In Asia

Convergence of GMP Compliance Qualification Programs

- Convergence of document assessment programs for GMP compliance qualification is desired to provide efficient use of time and resources.
- The variety of the necessary documents is left to the discretion of each regulatory authority, however, contents of documents such as Site Master Files (SMFs) can be converged based on the **PIC/S GMP guidelines/notes**.
- Those documents will be created and assessed with shared understanding among regulatory authorities, among industry members, and between regulatory authority and the industry.
- And if successful, it will lead to shorter assessment of the GMP compliance qualification.

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Issue Related To Submitting SMFs

- There are cases where regional guideline is followed to create SMFs.
- There are cases where Plant Master File (PMF) is required to submit at the time of new drug application. In some cases, PMF is required in addition to SMF
- Since required level of details of the SMF is not clear, there are cases where additional queries are made after the submission of the SMF.
- Other documents needed in addition to SMF for the GMP compliance qualification, are different for each regulatory authority. For example:
  - Checklist
  - Inspection Report
  - Additional data to PMF and periodical renewal of SMF
- There are only a few countries which require updating SMF.

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Suggestions from JPMA (1)

A. Convergence of the Contents of Necessary Documents

1. It is desired that the necessary contents in SMF would follow the **PIC/S SMF Guideline(*)**. (*)PE008-4"Explanatory notes for pharmaceutical Manufacturers on the preparation of a site master file"
   - Additional documents such as Plant Master File (PMF) or SMF based on regional requirement might be burden for industry because there are often cases that the content of such a SMF and PMF overlaps **PIC/S SMF Guideline**.
2. English will be used as the common language for documents of GMP compliance qualification.

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Suggestions from JPMA (2)

B. Promoting Operational Efficiency in GMP Compliance Qualification

1. It is hoped to have a more transparent assessment process for GMP compliance qualification:
   - Additional documents are often requested in order to aid understandings of GMP inspector.
   - However, the scope of the documents tends to be wider than that in the on-site inspection.
2. To avoid loss of evaluation time, it is desired that manufacturing sites will be evaluated by risk-based approach regarding both evaluation of documents and request of additional documents.
3. Moreover, it is desired that GMP qualification status of a manufacturing site will be mutually recognized among the regulatory agencies.

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Experience of Product Application from Japan to Asian Authorities

A Survey Conducted by JPMA

➢Purpose

- The purpose of this survey to JPMA participating companies is to highlight the difference of thinking toward SMF/PMF and to search “common denominator” for faster supply of innovative medicine to people in Asia.

➢Survey participant

- Survey was conducted to JPMA member companies and we received responses from 29 companies based on submitted documents in the past four years.

➢Outline of the survey

- In total 68 cases of NDA application to APAC-participating authorities were reported (Including same product to multiple countries) .
- Countries that requested to submit SMF/PMF at the time of NDA application were examined.
- Cases of additional queries and data requested from regulatory authority
- Presence or absence of on-site inspection

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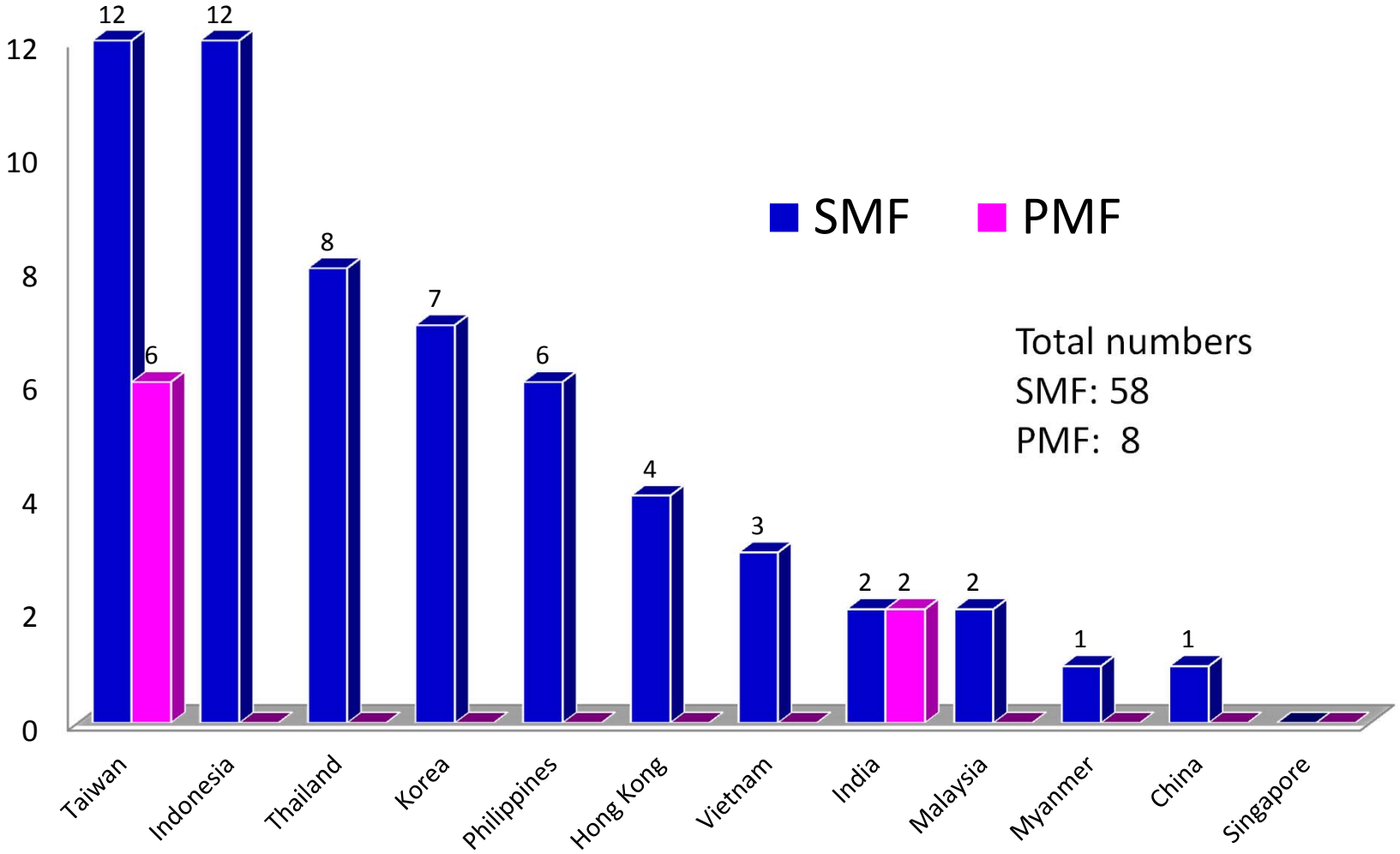
Asian Authorities Requested SMF/PMF at the time of Product Application



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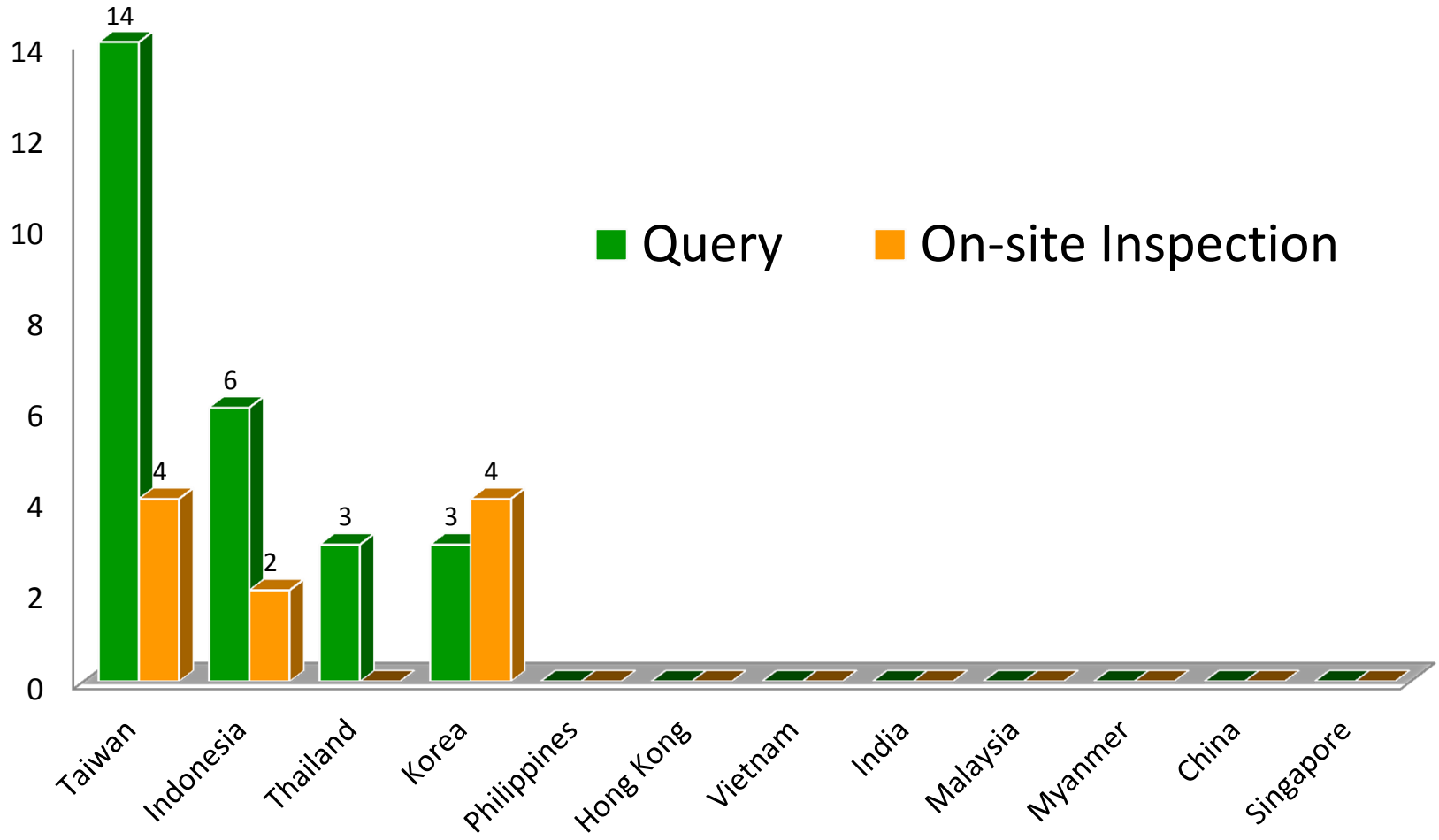
Query about SMF/PMF
And related On-site Inspection



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Query about SMF/PMF And related On-site Inspection

- Some regulatory bodies use submitted documents as the pre-reference for the on-site inspection.
- The condition/criterion for the selection of on-site inspection is not clear
- The relation between submitted documents and presence of on-site inspection is not clear.
- The process of GMP compliance assessment for manufacturing sites is not clearly defined.

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Draft SMF Template, prepared by PMDA

PIC/S
Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of A Site Master File
PE008-4

2.5 Product Quality Reviews

- Brief description of methodologies used

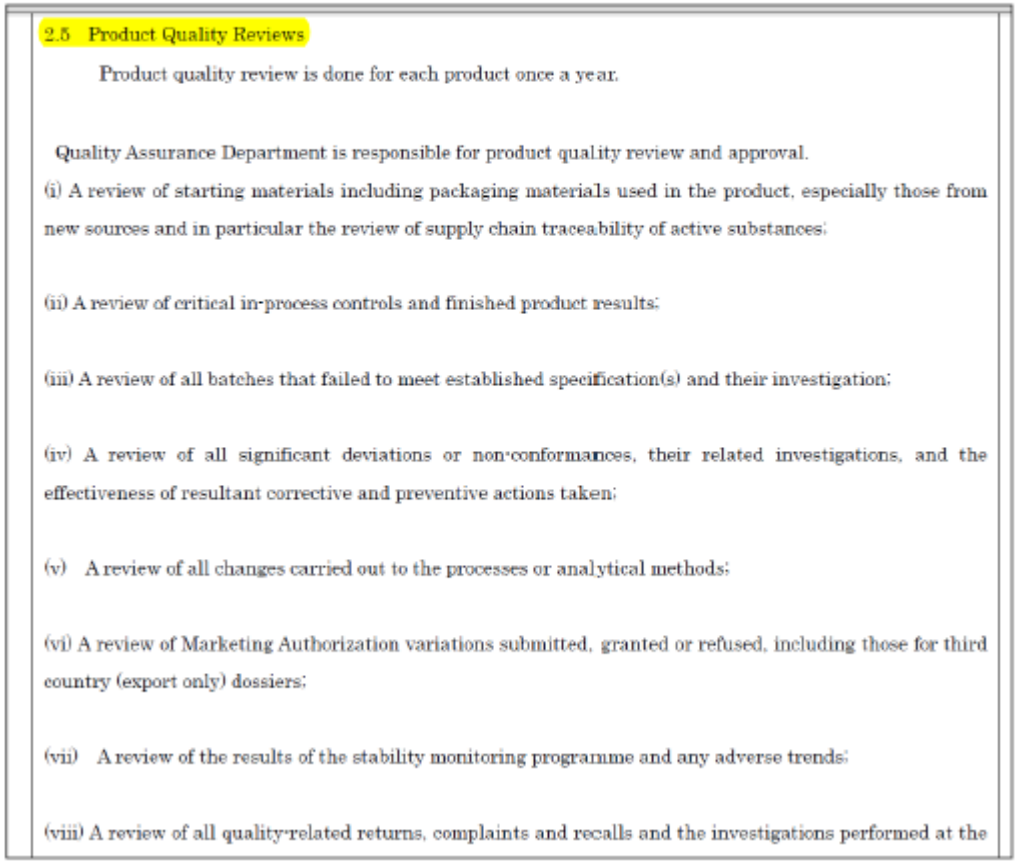
3. PERSONNEL

- Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 5, including senior management and Authorised Person(s) / Qualified Person(s);
- Number of employees engaged in the quality management, production, quality control, storage and distribution respectively.

4. PREMISES AND EQUIPMENT

4.1 Premises

Draft SMF Template prepared by PMDA



2.5 Product Quality Reviews

Product quality review is done for each product once a year.

Quality Assurance Department is responsible for product quality review and approval.

(i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances;

(ii) A review of critical in-process controls and finished product results;

(iii) A review of all batches that failed to meet established specification(s) and their investigation;

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;

(v) A review of all changes carried out to the processes or analytical methods;

(vi) A review of Marketing Authorization variations submitted, granted or refused, including those for third country (export only) dossiers;

(vii) A review of the results of the stability monitoring programme and any adverse trends;

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the

The template includes granularity to the Notes on preparation of SMF from PIC/S with further details to align the content to be written in the SMF

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Consensus of ATIM Session in 2018

Site Master File (SMF)

- Regulators and Industries have reviewed the SMF template, and reached the consensus to use it.

(SMF template have been informed & discussed in PIC/s Committee Meeting in Geneva, April 2018 as regional initiative actions.)

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Expectation of Product Lifecycle Management

- **Regulatory globalization (ie PIC/S)** allowed mutual-use of the data of Pharmaceutical development.
- The envisioned post-approval 'operational flexibility' by enhanced approach (ie QbD) as in **ICH Q8-Q11.**
- Achieving the innovation and continual improvement by assurance of Control Strategy and CPP

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For the Product Lifecycle Management

- Endorsement and recognition by the global standards is a beneficial for the industry to consider India as a reliable option when considering product lifecycle
  - Use of SMF as a first tool from PIC/S guidelines for GMP and Quality management
  - Use of ICH guidelines for scientific and risk management and GMP operations
- Use of ICH Q10 (pharmaceutical quality system) and ICH Q12 (pharmaceutical product lifecycle, *draft*) could be powerful tools to be used as common guideline

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Thank you

Japan Pharmaceuticals Manufacturers Association
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