APIC Active Pharmaceutical Ingredients Committee

# Secure Supply and Quality Control of Active Pharmaceutical Ingredients for Japan generic market

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# Secure Supply & Quality Control of APIs* for JP generic market

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# Secure Quality Control of APIs

**The current worldwide API sales context is as follows:**

- **Constraints of API manufacturers** facing the business model evolution**:**
  - Mandatory extension of marketing territories to be competitive & sustainable.
  - Only one quality worldwide
  - Continuous change and increase of Health Authorities (HA) requirements worldwide especially in emergent countries.

- **Agreement for a harmonized worldwide Reference Quality standard:**
  - "The International Council on Harmonization (ICH) brings together **Regulatory Health Authorities of Europe, Japan, United States, Canada, Switzerland** and experts from **Pharmaceutical Industry** to agree scientific and technical aspects of pharmaceutical product registration.
  - Would lead to the elimination of unnecessary delay in the global development and availability of medicines while maintaining safeguards on quality, safety, efficacy and regulatory obligations to protect public health".

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# Secure Quality Control of APIs (cont'd)

- **Applying ICH standards is a guarantee of Quality control for APIs**

APIs manufactured in Europe must comply with ICH guidances:

- **Related to Quality attributes:** Stability testing (ICHQ1), method validation (ICHQ2), Impurities/Residual solvents/ elemental impurities (ICHQ3), Pharmacopoeia (ICHQ4), specifications (ICHQ6)

- **Related to Quality Assurance system:** Good Manufacturing Practice for Active Pharmaceutical Ingredients (ICHQ7), Pharmaceutical Development (ICHQ8), Quality risk management (ICHQ9), Pharmaceutical Quality System (ICH10), Development and Manufacture of a drug substance (ICHQ11)

- **Related to the content and format of a Registration dossier** of pharmaceuticals for human use: the **Common Technical Document (CTD).**

Japan is part of ICH. Japanese Health Authorities agreed ICH standards. But, for registration dossiers & more especially for J-MF, Japan put in place different rules.

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# Secure supply

- The purpose of a **"Post approval change registration guidance"** is to define clear rules and identify the supportive data to provide as guarantee that the change proposed by the manufacturer doesn't affect the quality, efficacy of the product and safety of patient compared to what is described in the approved dossier.

- **Industry needs continuously to change existing dossiers** for Process and Analytics improvements (**e.g**. ***State-of-the-Art technology, operator security, …)*** and to face unexpected events (**e.g**. ***equipment breakdown, supply disruption of a raw material/ Starting material/ intermediate,…***).
  One chemistry change corresponds to dozens/ hundreds of Marketing Authorization Application dossiers worldwide.

- "Post approval change registration procedure" is absolutely **KEY to secure supply of a market** and to avoid potential shortage <u>putting at risk the health of patients</u>.

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# Secure Supply

- Based on more than 10 years of experience of European API manufacturers, JP post approval change procedure is too often based on a **case by case assessment** which slows down significantly the approval.

- **A detailed guideline on JP post approval change management** would help a lot API manufacturers and probably PMDA assessors, limiting misinterpretation, regulatory non compliance and saving time.

- Basically **Generic DP dossiers only make a cross-reference to Manufacturing process section of JMF**. A guide on the maintenance of this section is defined in the Japanese regulation.

- For Specifications & Tests section, it is not clear. We use more and more **"Simple consultation procedure"** which is very appreciated and useful but the decision is provided explicitly **only for one special case**.

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# Secure Supply

- The existing JP guideline for Manufacturing process section of JMF **is not consistent with existing guidances from ICH member states:**
  - In Japan, **a major change** ( **PCA**) needs before any approval around **12 months in practice.**
  - In most of the cases a **process change** even at early step in the chemical synthesis is assessed as a major change in Japan compared to minor change or annually reportable in European and US regulations.

- **Reclassification of some process changes to minor ones** would mitigate the regulatory burden when final quality of the API is not impacted as it is currently in place in Europe and US.

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# Secure GMP level of API manufacturers by local Regulation

- APIs must be manufactured in Europe according to **European law** for **Good Manufacturing Practices** consistent with international guidances:
  - **[EU GMP] – European Commission – Eudralex Volume 4 – EU Guidelines to Good Manufacturing Practice, Part II: Basic Requirements for Active Substances used as Starting Materials**
  - *[ICH Q7] – International Conference for Harmonization - Good Manufacturing Practice for Active Pharmaceutical Ingredients*
  - *[WHO TRS 961 annex 3] – World Health Organization - Technical Report Series - Good Manufacturing Practices for Pharmaceutical Products.*

- The main challenge for a manufacturer is to ensure **continuous** GMP compliance whatever the event occurring during production.
  ***e.g. Out of Specifications (OOS), deviation, disruption of raw material, change of starting material, equipment failure, …***
- Facing such event is the "**normal life**" of any API or DP manufacturer

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# Secure GMP level of API manufacturers by local Health Agency inspections

- **European Health Agencies organize regular inspections** to check the compliance with European GMP rules:
  - Regularly, once per 3 years for most of European countries,
  - Up to each year for sites manufacturing several APIs.

- European Health Agencies organize more often **unexpected site inspections** to be closer to US FDA ways of working from 2015.
  ***e.g. ANSM France, around 4 days of unexpected site inspection.***

- In accordance with a **risk management approach**, European Agencies adapt the frequency of the inspections based on their knowledge of API manufacturers ***e.g. Track records***.

- US FDA intends to implement in 2016 similar approach based on ***Quality metrics.***

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# Secure GMP level of API manufacturers by local Health Agency inspections

- In Japan, beside a site inspection based on a quite similar risk management approach, **GMP compliance reviews** or paper inspections were put in place per API in 2 different contexts:
  **Periodically** (5 years) & in case of **Major change** of a registration dossier (**PCA).**

  - **Periodical GMP compliance review**: In practice, several months are needed before closure. Repeated documentation requested for each paper inspection even for several APIs coming from same site. Several set of questions & answers before common understanding.

  - **Pre-approval GMP compliance review** in the context of PCA (partial change approval): Many requested data are already given in periodic GMP compliance review & in the updated FMA (Foreign Manufacturer Accreditation).

- Unnecessary **duplicated work** and time consuming for both parties
- **Mix up between GMP inspection and registration procedure** slowing down post approval change. Not at all applicable in Europe and US.

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# Secure GMP level of API manufacturers by local Health Agency inspections & MoU

Systematic paper GMP compliance reviews, very demanding in terms of workload and time consuming for both parties, interfering with registration procedure, increase the risk of disruption of the supply.

- ***Would it be possible :***

  ***1) At least to simplify, rationalize GMP compliance reviews, archiving global information on Quality Assurance system of manufacturing sites at PMDA to be shared between assessors avoiding redundant inquiries?***

  **2) To extend GMP Memorandum of Understanding (MoU) for APIs between some European countries and PMDA based on a recognition of an equivalent GMP level standard?**

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# Conclusion

- **Inspection at site level** is the most preferred option by EU Industry.
- **Paper inspection for Japan could be simplified** avoiding many redundancies.
- A “mutual recognition procedure” as **GMP Memorandum of Understanding (MoU)** between PMDA and some European countries applying fully ICH standards would avoid potential supply disruption while maintaining same guarantees on GMP compliance.
- Regulatory burden should be mitigated when API quality is not impacted especially in the context of **post approval change registration dossier.**

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# Conclusion (cont'd)

- **MHLW notification dated in 2016: January,19th & February,12th** give us a good chance to correct discrepancies due to miswriting and mistranslation of our J-MF and upgrade the "Dossier Compliance" in Japan.

- **Reinforced collaboration between Industry & Health Authorities** based on a better understanding of mutual constraints could help to improve the efficiency of the Post approval change Regulatory Procedure. APIC would suggest working group.

- Beside Quality Control of APIs and GMP compliance **stable supply is key to protect public health.**