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# Post approval change of Japanese registration dossiers and impact on market supply

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# Business model evolution of API sales

**Worldwide**
**Economic context**

- Economic crisis/ Government policies/ Cost of Medicines.
- Mandatory extension of marketing territories to be competitive.
- Strong competition between API manufacturers.

**Worldwide**
**Regulatory context**

- Recent Human drama further frauds & counterfeits.
- Drastic increase of Health Authorities (HA) requirements worldwide especially in emergent countries.
- Continuous changes of HA requirements
- HA inspections (site/ paper) increase.

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# Business model evolution of API Sales

- **Regulatory Affairs has become key part of the industrial strategy for marketing Medicinal & Food additive products:**
  - Motor/dynamic of the marketing strategy:
    - **Mandatory exercise to get approval for sale**
    - **Best performance, quicker approval**
    - **Central in the evolution of our business model even for existing products**
  - Very early in any project in parallel of economical and technical feasibility
  - Specific: Ethics, Generics, CHC….to identify the most efficient strategy
  - Pro-active allowing anticipated decisions (Regulatory Intelligence)

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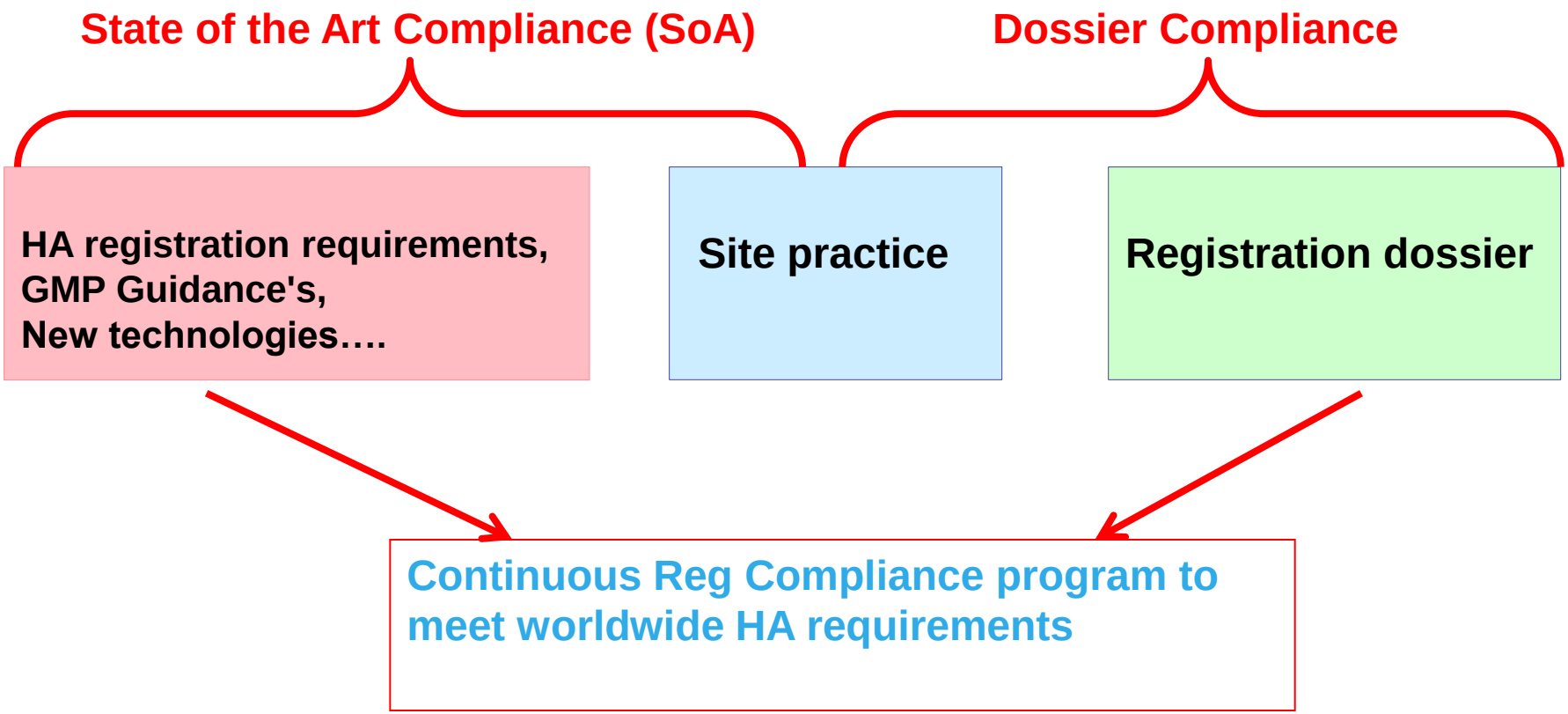
# Challenge on Regulatory Compliance






HA: Health Authorities

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# Risks of Regulatory non compliance

- **Critical "dossier non compliance" issues:**
  - Company image**:** A deficiency on 1 dossier from 1 manufacturing site can impact all other dossiers from all other manufacturing sites from the same company (doubt on reliability).
  - Recall of batches already on the market.

- **Critical "SoA non compliance" issues:**
  - MAA withdrawn in Europe at quinquennial MAA renewals
  - Loss of "GMP certificate" for API or DP manufacturers after HA **i**nspections**.**
  - Warning Letter, Loss of Authorization to import to US after FDA inspection

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# Risks of Regulatory non compliance

- **Inappropriate management of change control:**
  - Huge increase in regulatory requirements leads to heavier management of post-approval changes of our dossiers.
  - Find a balance between necessary changes for process improvement (State-of-the-Art technology, safety, cost, double sourcing of material) and Regulatory burden.
  - One chemistry change corresponds to dozens/ hundred of MAA dossiers worldwide. Consequently, delays, blocked products (batches in quarantine) linked to Authorities assessments increasing the risk of supply disruption and potential shortage of the markets.

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# Risks of Regulatory non compliance

- **Greater risk in Japan to be non regulatory compliant when compared to other countries**

  PAL procedure from April 2005 with specific JP requirements to manage in parallel at least 3 different documents is particularly challenging:

  - J-MF procedure for API different from CTD format compared to other members of ICH.
  - Foreign Manufacturing Site Accreditation (FMA) per process.

  **E.g.1: Manufacturing site can have more than 1 FMA.**

  - GMP compliance review or paper inspection **per API** in 2 different contexts: **periodic** (5 years) & in case of **PCA.**

  **E.g.2: Paper inspections for same API the same year. Several paper inspections the same year for the same manufacturing site.**

  **E.g.3: Paper inspection for a manufacturing site closed for several years.**

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# GMP Compliance review or paper inspection

- **Paper inspections**: In practice, this procedure may last several months:
  - Repeated documentation requested for each paper inspection. Especially when the manufacturing site owns several J-MF (Site organization, SOP list, key SOP as CC, OOS management, ….).
  - Several set of questions & answers before understanding.
  - Unnecessary duplicated work and time consuming for both parties.

  ***APIC suggestion*:** simplification procedure based on a risk assessment of the manufacturing site as it is currently done in Europe and US by Health Authorities.

  **E.g. Track record (knowledge from PMDA) of the site.**

- **On-site inspections:** this is far the preferred option of the European industry. PMDA inspectors are always welcome on our API manufacturing sites.

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# GMP Compliance review or paper inspection

- **Mutual Recognition Agreement (MRA) between European countries and PMDA or more exactly GMP Memorandum of Understanding (MoU) for APIs:**
  - Majority of European HA perform periodic inspections at site level.
  - These inspections cover topics requested by PMDA

  This would mean no need for paper inspection any longer.

  **E.g. MRA with Germany**

  ***APIC would suggest*** *that MHLW/ PMDA extend MRA to more European countries.*

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# GMP Compliance review or paper inspection

- **High risk of confusion (mix up) between GMP inspection and J-MF documentation:**

  No other example worldwide.

  Pre-approval GMP inspection in the context of PCA (partial change approval).

  Many requested data are already given in periodic GMP compliance review, FMA and again in this pre-approval GMP compliance review.

  Unnecessary duplicated work and time consuming for both parties.

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## GMP Compliance review or paper inspection

Those regulatory procedures, very demanding in terms of workload and time consuming could lead to some disruption of the supply and consequently shortage of the Japanese market.

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# Particular J-MF requirements


- J-MF content (module 1) different from CTD format compared to other member states of ICH especially regarding **description of the manufacturing process.**

  **E.g. Process parameters as a range in Manufacturing Batch Record (MBR), CTD module 3 but as a set value in the Module 1.**

- Some chemical processes (robust processes) do not have **critical parameters**. However, JP regulation request to highlight critical parameters as a basic rule.

  **E.g. Monitoring parameters are not critical, with no impact on the quality of the final API.**

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## Particular J-MF requirements

Update of the 3 modules

- Difficulties to manage in parallel:
  - MBR according GMPs,
  - Modules 2 and 3 according ICH, and
  - Module 1 according Japanese standard.

- An **official English detailed guidance** would be appreciated by Industry for a better understanding of the Japanese rules to update modules 1, 2 and 3 of J-MF after a change. A case by case assessment could increase the risk of inconsistencies.

**E.g. Update of Module 3 seems to be optional in case of MCN and lead to a potential discrepancy between Module 1 and Module 3 which are both registered at PMDA.**

**E.g. Update of Module 2 is not well understood.**

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Consistency
Dossier & MBR

# Particular J-MF requirements

- Some "dossier non compliance": registered documentation compared to Manufacturing Batch records (MBR) observed during GMP compliance reviews could be avoided with consecutive regulatory burden.

**E.g.1: Process parameters as a range in MBR and a set value in the Module 1.**

**E.g.2: Discrepancies between Module 1 & Module 3**

**E.g.3: Inconsistencies between MBR/ Module1/ Module3**

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# JP post approval change dossier procedure

- A major change ( PCA) needs as a standardized timing for approval, between 12 and 18 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. 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.

- Especially we would appreciate that **monitoring parameters** with no impact on the quality of the final API, should be assessed as minor even in the case we do not have any other critical parameter to declare.

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# JP post approval change dossier procedure

- Blocking situation in case of **2 parallel PCA for the marketing authorization holder ( MAH)** might increase the potential risk of disruption of supply and consecutive shortage on the Japanese market**.**

**E. g. When a MAH refers to two J-MFS from two different suppliers, a PCA triggered by supplier A blocks any partial change by supplier B (competition issues).**

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# Post approval change procedure in Europe

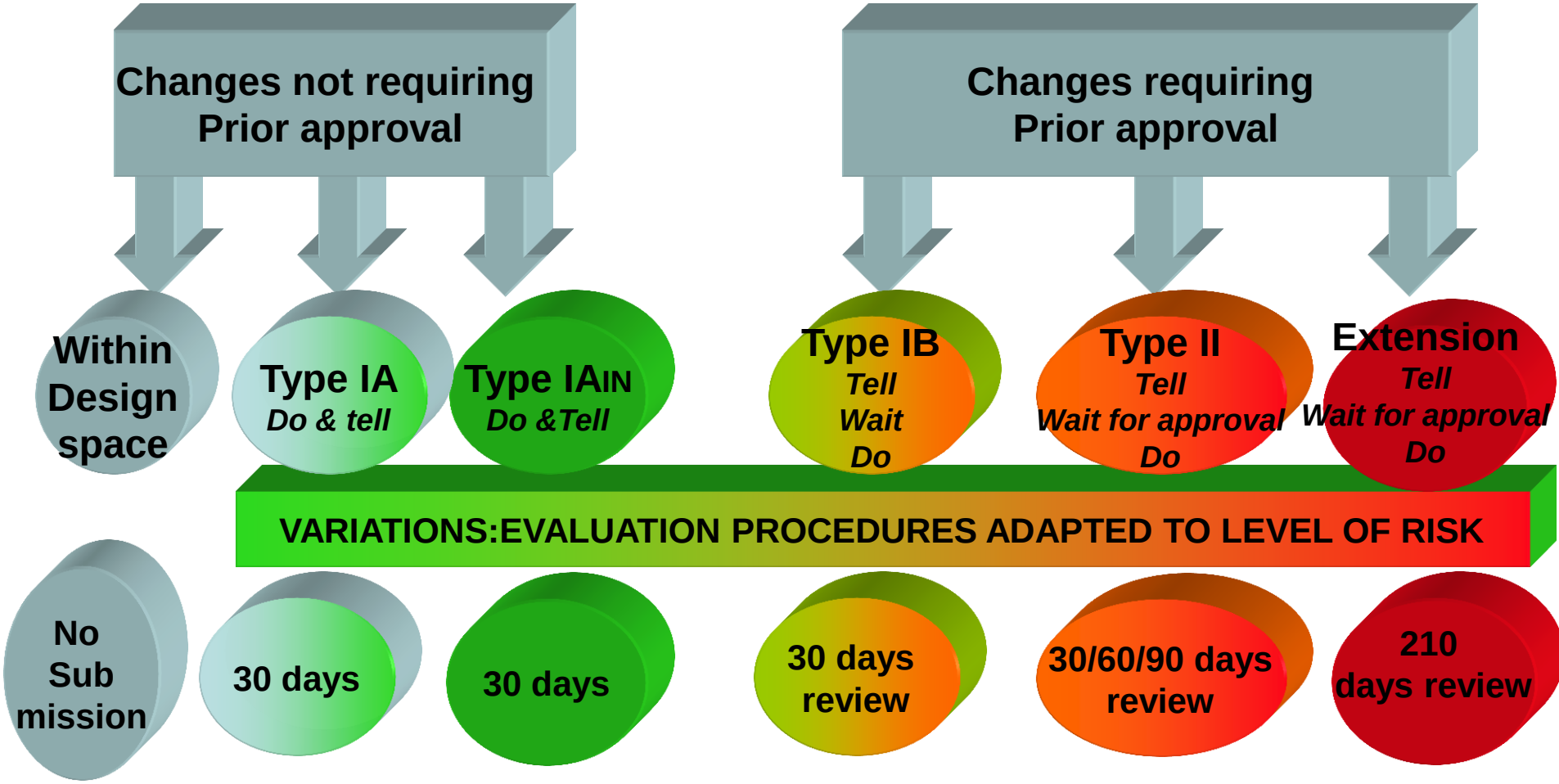
- Regulatory impact on pharma registration dossier depends on the **risk assessment of the change** on API Quality, efficacy of the medicinal product and safety of patient. Standardized timing of approval is adapted and graduated to this risk.

- Regulatory impact depends on API registration procedure. It will be reduced in case of CEP.
  - **ASMF*:** in support of a marketing authorization application (MAA) for a medicinal product and is reviewed only when a MA application refers to it.
  - **CEP***: A CEP is granted, after **evaluation as a standalone dossier**, by EDQM (European Pharmacopoeia). The CEP certificate once granted by EDQM is used in the MAA in place of full information on the substance. CEPs are recognised by Member States of the European Pharmacopoeia Convention and by the European Union. Other countries (> 20) have also chosen to recognise them.

    **Note: CEP is the preferred option by the EU Authorities if API is registered in European Pharmacopoeia.**

*ASMF: Active Master File * CEP: Certificates of suitability of monographs of European Pharmacopoeia

# European Guideline on variations 16.05.2013C (2013) 2804



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# Post approval change dossier procedure in Europe

- "Guidelines of 16.05.2013 on the details of the various categories of variations, in addition to Commission Regulation (EC) No 1234/2008 of 24 November 2008 on:
  - **A. ADMINISTRATIVE CHANGES: variations 1-7**
  - **B. QUALITY CHANGES: variations classified per category**
    - **B.I. Active Substance**
    - a) Manufacture
    - b) Control of active substance
    - c) Container closure system
    - d) Stability
    - e) Design Space and post approval change management protocol

For each change proposed, this guideline indicates:
- Conditions to be fulfilled
- Documentation to be supplied
- Procedure type

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# Post approval change dossier procedures

## Examples of assessment of post approval changes in different regions

## Japan / Europe / USA

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# Comparison of post approval change MAH dossier procedure

- **Increase of batch size of final substance or intermediate up to 10-fold**
  - Any changes to the manufacturing process are only those necessitated by scale-up
  - Reproducibility of the process not affected
  - Specifications remain the same
  - Quality of the product not affected

| | JAPAN | EUROPE | USA |
|---|---|---|---|
| Chemistry dossiers | **Amendment of J-MF**<br>• Batch analysis data from 3 API batches<br>• Process validation | • **Amendment of ASMF or**<br>• **Annual notification* of CEP:** Analysis data of 2 API batches | **Amendment of US DMF:** Batch analysis data of 3 API batches |
| Marketing Authorization Holder (MAH) | **Minor Change Notification** | • **Annual notification of a Minor change** (variation IA) if cross referred to an ASMF<br>• **No regulatory action** if cross referred to a CEP. | **Annual notification of a Minor change** in the Annual Report |

Minor Change Notification of the MAH* dossier **within 30 days further implementation date**. However when several customers refer to same DMF it may take several months before supplying batch impacted by the change.

**API can be used immediately whatever CEP or DMF (Eu/US) registration dossier for API**

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# Comparison of post approval change MAH dossier procedure

- **Change in the concentration of a reagent used in the manufacturing process**
  - Reagent used for pH adjustment in a reaction step
  - Concentration changed: **e.g. from "*NLT 25%*" to "*NLT 23.5% to NMT 26.5%*"**
  - Quality of the Intermediate and Final API not affected
  - Qualification and validation work performed as appropriated

| | JAPAN | EUROPE | USA |
|---|---|---|---|
| Chemistry dossiers | **Amendment of J-MF** | • **Amendment of ASMF**<br>• **Annual notification to CEP**<br>Analysis data of 2 API batches | **Amendment of US DMF:**<br>Analysis data of 3 API batches |
| Marketing Authorization Holder (MAH) | **Partial Change Application**<br>**Review period:**<br>**12 months** | • **Minor change** ( variation IB) if cross referred to ASMF<br>• **No regulatory action** if cross referred to a CEP. | • **Annual notification of a Minor change** in the Annual Report if early step or<br>• **Notification and implementation** (CBE30) if demonstration of equivalence done at least at the final intermediate |

**API can be used at latest 30 days after MAH submission.**

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# Comparison of post approval change dossier procedure

- **Change/addition of a manufacturing site for the API**
  - Manufacturing sites belongs to the same company and have the same quality system in place
  - Both sites have the same manufacturing process and controls in place
  - Quality of the product manufactured in both sites is identical
  - Qualification and validation work performed at both sites

| JAPAN | EUROPE | USA |
|---|---|---|
| **New J-MF/ Amended J-MF** | **New ASMF/ Amended ASMF**<br>**New CEP/ Amended CEP** | New DMF/ Amended DMF |
| Partial Change Application<br>Review period: **12 months** | **Immediate Notification** (variation IA IN)<br>Review period: **30 days** | **Moderate change**<br>Changes being effected - CBE30<br>Review period: **30 days** because the site has been inspected within 3 years with equivalent process . |

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# JP Pharmacopoeia & equivalence to other EU-US Pharmacopoeia

- **Japanese analytical methods and PMDA requirements:**

  Recognizing equivalent analytical methods (European/US Pharmacopoeia methods) with the Japanese pharmacopeia monograph is of high importance for industry.

  Would it be possible to receive an official statement to confirm that it is now accepted by PMDA to avoid any ambiguity and assessments made case by case?

  Of course this recognition should be based on a full package of validation data.

  **Note: This is already officially accepted by the Japanese Pharmacopoeia**

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# Conclusion

- Many regulatory non compliance are due to **misunderstanding** on JP Regulation because very specific compared to international guidance's on harmonization of scientific and technical aspects.

- **Detailed guideline on JP post approval management** would help a lot API manufacturers and will avoid misinterpretation and inconsistency between dossiers.

- **Rules on update  of JP registered modules** are not well understood and can lead to inconsistencies between them and compared to MBR reviewed during GMP Compliance review.

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## Conclusion (cont'd)

- **Regulatory burden** should be mitigated when API quality is not impacted especially in the context of post approval registration dossiers.
- **Inspection at site level** is the most preferred option by EU Industry.
- **MRA with other European countries** would avoid long delays before approval of paper inspections and potential supply disruption while maintaining same guarantees on GMP compliance.

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## Conclusion (cont'd)

- **State of the Art of API registration dossier** is a pre-requisite and not in the scope of this presentation. It is the duty of an API manufacturer to provide all guarantees in term of Quality and efficacy of the product.

- No compromises when patient safety is at stake. Stable supply is also key to protect public health. Reinforced collaboration between Industry & Health Authorities based on a better understanding of mutual constraints could help to improve the efficiency of the Regulatory Procedure.