La compliance nell'importazione di starting materials e intermedi

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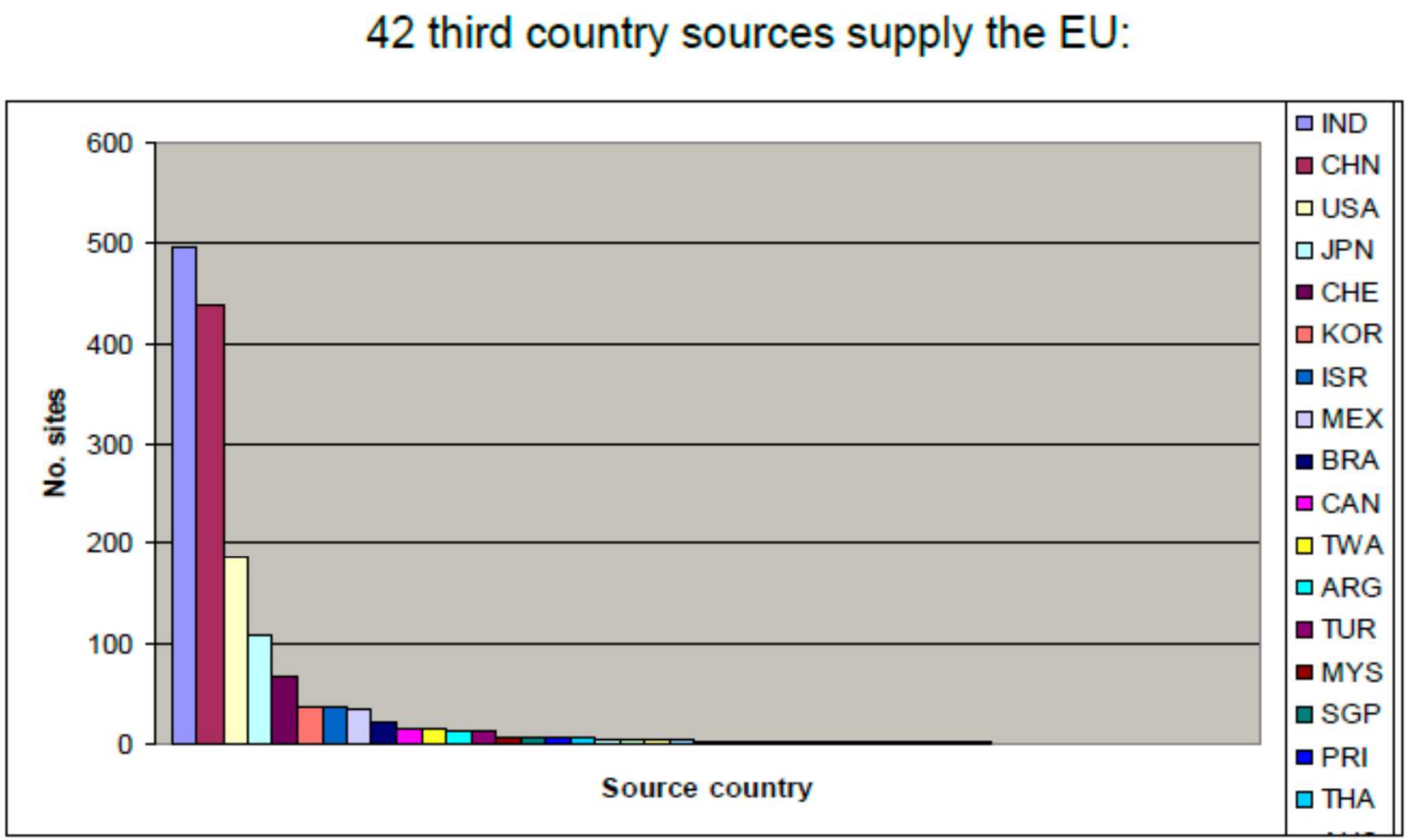
Agenda

- **Introduction**
- **Legislation**
- **Life-cycle**
- **Conclusions & comments**

Why supply chain in compliance?



Source: MHRA

Why supply chain in compliance?

TIANJIN ACCIDENT

"**The accident at Tianjin** that was probably due to **improper storage of hazardous materials** can be the cause for not being able to ask for earlier resumption of production than that contemplated by the local authorities for the entire industrial park at Chizhou .
We were informed by NFTZ Alchem immediately after the accident that all local Safety Departments were notified by Beijing Authorities to step up safety inspections of dangerous chemical production, transportation, storage and logistics nationwide… (December 2015)

Why supply chain in compliance?

Verifica Officina Farmaceutica: Divi's Laboratories Ltd. (India) (24/03/2017)

Avviso alle Aziende Farmaceutiche

Si richiede alle Aziende titolari di AIC di medicinali ad uso umano e/o alle Aziende produttrici di medicinali destinati al mercato comunitario o all'esportazione in Paesi terzi di verificare se, per i loro medicinali autorizzati e commercializzati per il mercato italiano ed europeo, ovvero prodotti per l'esportazione, risulti come fornitore di principi attivi/intermedi di produzione l'Officina Farmaceutica:

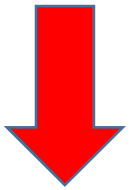
Divi's Laboratories Ltd. (Unit II), Chippada Village, Annavaram, Bheemunipatnam Mandal, Visakhapatnam District, Andhra Pradesh - India.

SOLO le aziende che hanno un riscontro positivo, dovranno darne comunicazione e indicare l'eventuale presenza di siti di produzione di principi attivi/intermedi alternativi a quelli in oggetto per i medicinali autorizzati o prodotti per l'esportazione.

Si richiede, da ultimo, per i medicinali autorizzati con procedura di Mutuo Riconoscimento, di specificare il codice di procedura europeo

Supply chain & Recent Legislation

- Written confirmation (Directive 2011/62/EU)
- QP declaration (May, 2014)
- Certification by a Qualified Person and batch release (April, 2016)
- GDP
- Enforcement of chapter 5 of EU GMP part I



strengthen obligations and supervision
on API manufacturers

QP declaration versus API impact

- Declaration template states that

the active substance has been manufactured in accordance with the good manufacturing practice for human and veterinary use part II

- The QP declaration should be based on **an audit of the active substance manufacturer**

It is established as a good practice that the audit should be conducted at the manufacturing site, i.e. on site audit

- Audits should be by, or on behalf of, suitable trained and experienced person, **who might be a third party contractor**

- The GMP basic requirements for active substance used as starting material are applied with **the first use of the starting material**

(as designed in the quality section/ module of the regulatory submission)

Template

PART A: Concerned active substance manufacturing sites

Name of Active Substance:

Name and Address of Active Substance Manufacturing Site[1,2]	**Manufacturing Operation / Activity[3]**

1. List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material, include intermediate manufacturing sites / part–processing sites.

2. State the site name and address in detail, including the building numbers (if applicable).

3. For example – Full or partial manufacture of the active substance, micronisation.

PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

This QP declaration is applicable to the following registered MIAH(s), that use the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product, where the active substance is registered as a starting material and is manufactured at the sites listed in Part A:

MIAH Site	**MIAH Number**	**Manufacturing Activity**

PART C: Basis of QP Declaration of GMP Compliance

Please tick section (i), complete the table in section (ii) and, if applicable, add the supplementary supporting information to section (iii).

(i) ☐ On-site audit of the active substance manufacturer(s)

(ii) Audit(s) of the active substance manufactured at the site(s) listed in PART A has/have been completed either by the MIAH(s) listed below or by a third party auditing body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s) as listed:

MIAH Site (or contract giver)	Auditing body (contract acceptor)	Site audited	Date of audit[4]

4 Justification should be provided if the date of last audit exceeds 3 years:

QP certification and batch release versus API impact

The annex has been released to reflect the "supply chains globalization"

- The certification certifies that the batch is in **compliance with GMP** and its **requirement of MA**
- The **entire supply chain of the active substance** and medicinal product up to the stage of certification is **available,** including **the manufacturing sites of the starting materials**
- **All audits involved in the manufacture of the active substance have been carried out** and all the audit reports are available to the QP

EU GMP chapter 5 vs. API impact

*In **March 2015** a new section has been added to reflect the legal obligation of MAH that active substances are manufactured in GMP . Specifically for API supplier:*

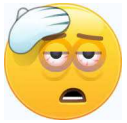
- **Level of supervision** should be **proportionate to the risks** posed by the individual materials
- Appropriate aspect of production, testing and control, including handling, labelling, packaging … should be documented in the a **formal Quality Agreement** or specification
- **Supply chain traceability** assessed and periodically verified
- **Audits** carried out and CAPA put in place and implemented; routine audit plan based on risk assessment

Responsibilities

- **MAH has the ultimate responsibility** for the performance of medicinal product over its lifetime

- **The QP of the medicinal product** is responsible to ensure the compliance of each individual batch

- **The QP of the medicinal product**, signing the declaration, is confirming that these statements are correct and are the basis by which the regulatory submission may be approved



API SUPPLIERS ?

Main consequences for API manufacturers

- Disclose **name of suppliers and address of API starting material**

- Disclose **every details of API intermediates** suppliers and allow for inspection by MAH

- **Accept Technical Agreements** with customers

Changes : a concrete example (life-cycle)

1. The synthesis only covers one chemical transformation step and purification, which is not considered acceptable. The proposed starting material, [redacted] is very close in structure to the final substance and is not acceptable. The described synthesis should include multiple synthesis steps to ensure that the possible impurities in the starting material are removed and GMP must also be followed from an early point in the synthesis to ensure consistent quality of the active substance.
   Therefore, ASM should propose new starting materials further back in the synthesis and update all relevant sections of the ASMF (including detailed information on synthesis and manufacturing, flow schemes, IPC testing, starting material specifications and intermediate specifications etc.).
   The impurity discussion has to be updated and should include, for each proposed starting material, a discussion and summary of experiments on origin and fate of impurities. It should be demonstrated that all potential impurities are controlled by suitable controls in isolated intermediates or final active substance.

4. According to CPMP *Guideline on the Chemistry of New Active Substances* the starting material suppliers and the flow chart, indicating the synthetic process prior to the introduction of the starting material, have to be included in the updated DMF section 3.2.S.2.3. In the future, any change of the starting material manufacturer has to be applied for with a variation application.

Redefinition of the starting material

according to the new guidelines – Impacts for API supplier

- Change to the condition of the MA, with the identification of new starting materials suppliers
- Extension of GMP requirements
- On site audit and CAPA requested in a very limited timing for API supplier and MAH (harmonization?)

Changes to starting materials and intermediates

Rif. 1234/2008 and Changes to an approved NDA /ANDA

Change type	US	EU
Change of a supplier for an intermediate before the final intermediate	CBE	1B
Change of a supplier for a final intermediate	PAS	1B
Addition of a supplier for a KSM	Annual update or CBE	1AIN or 1B

Consequences

- Changes to intermediates supplier are critical under many points of view and different level of requirements:
  - Knowledge of the manufacturing process description (including reagents and catalyst) for the preparation of the DMF updates
  - Change control with Impact assessment
  - Audit in place for assessing the GMP status to support the QP declaration and the Batch release certificate – CAPA plan

- Changes to key raw material supplier are deemed less critical. Complete qualification process according to the SOP is required.

Actions for API manufacturers

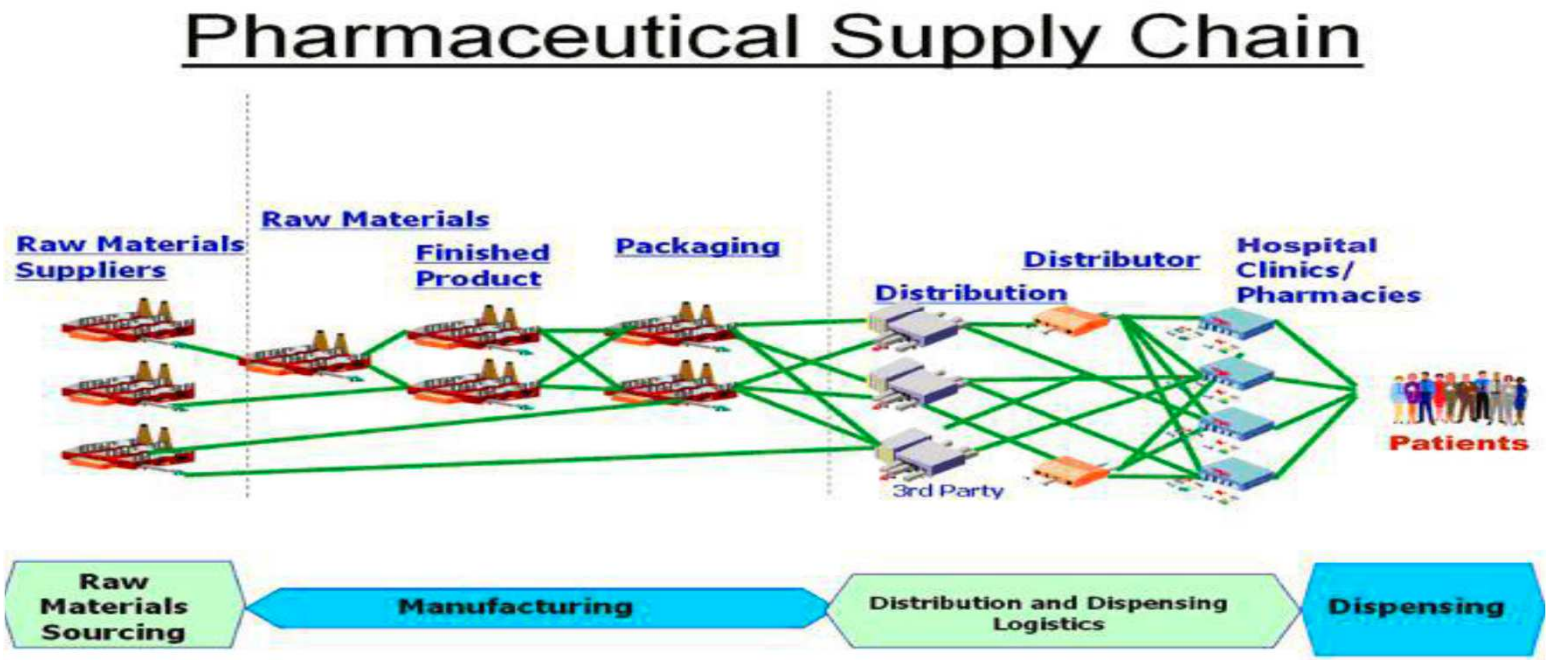
- **Supplier risk management tools**

Product name	NO active source	Single source	No reliable/ unstable source	Country risk	Low annual capacity	Production in 2016	Open regulatory issue	Perspective regulatory issue	Competition	Score
XXX1		X	X	X	X			X	X	6
XXX2		X		X		X		X		4
XXX3			X	X		X		X	X	5
XXX4				X			X	X	X	4
XXX5			X	X	X	X	X	X		6
XXX6		X	X	X		X		X		5
XXX7		X	X	X		X		X		5
XXX8		X	X			X		X	X	5
XXX9		X		X	X	X		X		5
XXX10	X	X	X		X	X		X		6

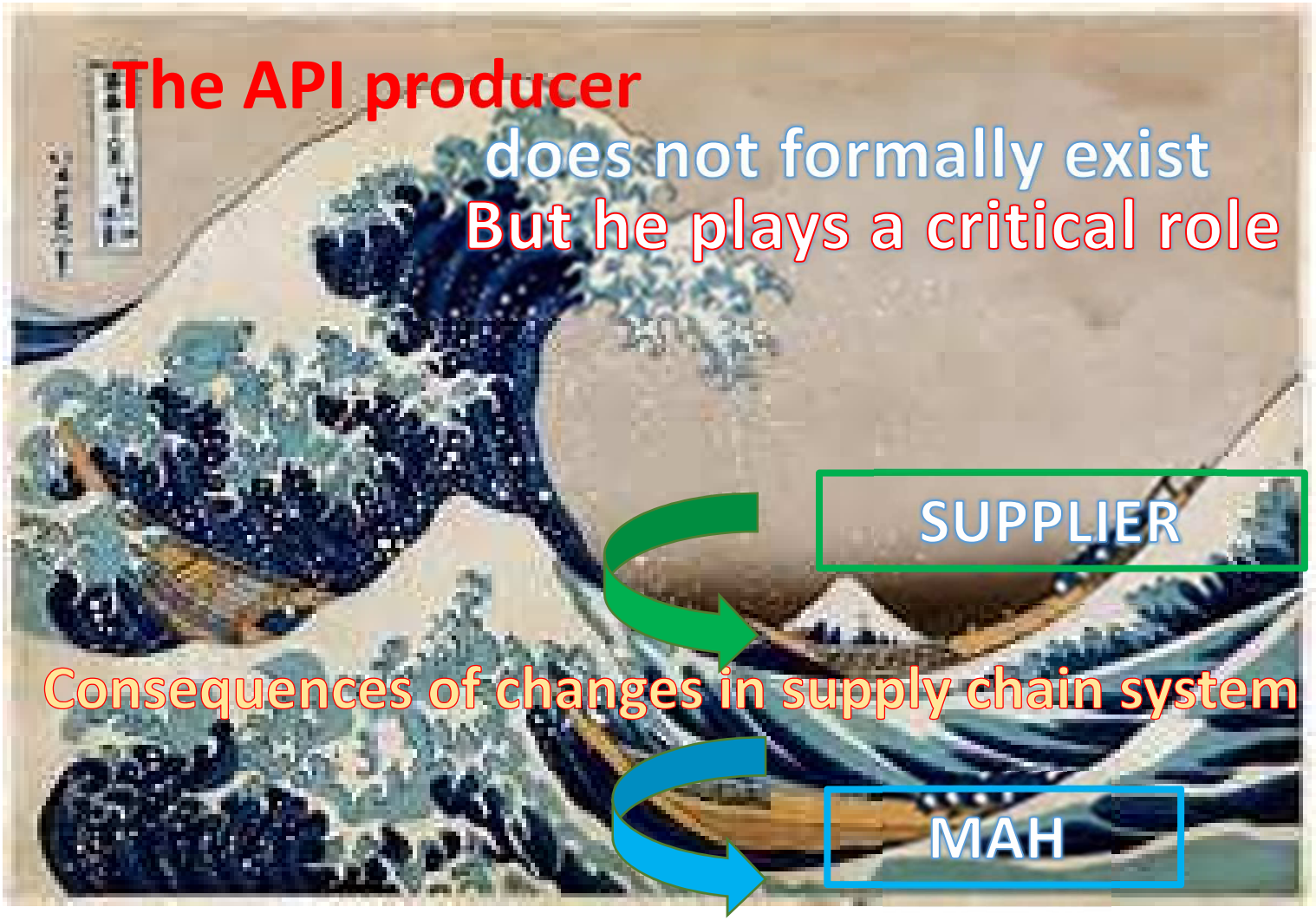
- **Increased budget** for yearly expenses on site audit plan

- **Technical Agreements** with intermediates suppliers

Supply Chain Challenges



Conclusions & Comments



Conclusions & Comments

❖**The API producer:**

- **does not formally exist**

  even if it represents a means through which the obligation can be guaranteed

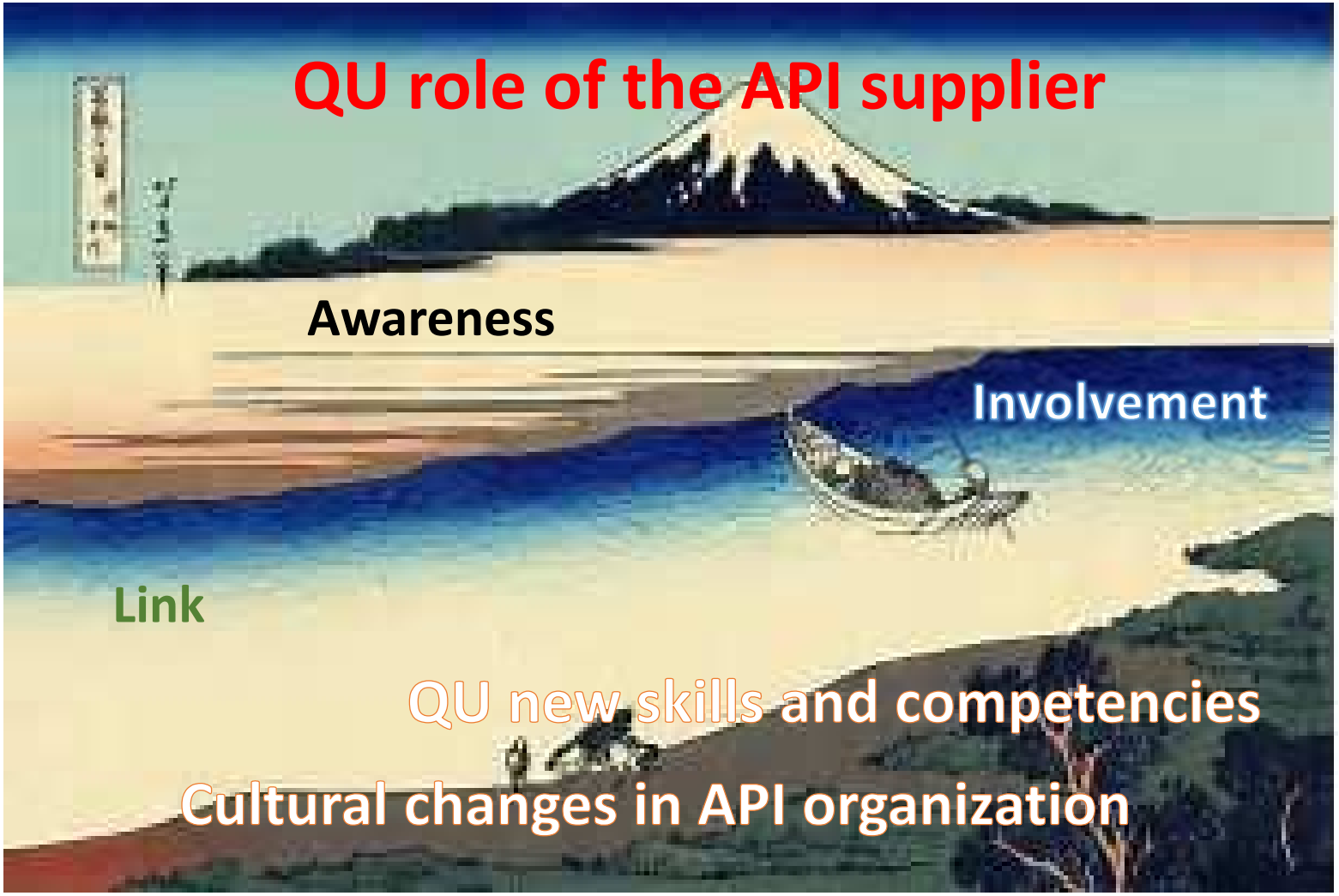
- **has to be aware of the identified regulatory starting material,** if he is not the holder of the ASMF

- **has to be aware of the consequences of changes in respect to supply chain system** if he is holder of the ASMF

- Must establish an effective and timely **change reporting from** the supplier

- Must establish an effective and timely **change reporting to** the MAH

Conclusions & Comments



Conclusions & Comments

❖ **Role of the QU of the API supplier:**

- **Awareness** and handling of the requirements and their management
- **Involvement** since the beginning in the supply chain management and sourcing strategies of the company
- **Link** between the Quality teams of the starting material and the pharmaceutical manufacturers

✓ **new skills and competencies in the QU**

✓ **cultural change in the API manufacturers organization**

Thank you very much

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