Assessment of API Supply Chain during GMP Inspection
Agenda

- Introduction
- Practical Examples
- Key Points
Introduction

- Exploring best practices in evaluating the integrity of API supply chains through the inspection of sites engaged in supply of active pharmaceutical ingredients and fabrication of drugs in dosage form

- How to select, qualify and follow up API suppliers?

- Who else is taking care of APIs from the supplier to the user?

- RISK: What could turn wrong?

- IMPACT OF RISK: What could be the consequences?

- MITIGATION OF RISK: Which control points and tools to mitigate the risk?
Practical Example 1: Protamine sulfate

- Most world sources of Protamine sulfate are located in Japan (sperm of salmon fished off the Pacific coast next to Fukushima power plant)
Practical Example 2: Quinine

- Since XVII\textsuperscript{th} century, quinine is extracted from Cinchona barks
- Cinchona barks is mainly sourced from DR of Congo
- DR of the Congo is politically instable
Practical Example 3: Strike

- There has been a strike of grain dock workers in Brazil.
  - The strike impacted goods such as coffee, sugar, corn and soybean
  - Possible impact on caffeine, amino acids, citric acid, ethanol, carbohydrates, peptone, polysorbate
Air and ship freight:

- Air freight: temperature control vs. security
- Air freight: what happens during transfer?
- Ship freight: temperature and humidity control?
Practical Example 4: some deficiencies

- “A list of approved suppliers was provided but this list was not managed as a Quality document”

- “In the form where all the information is collected, the address of the manufacturing site was not specified “: Manufacturer vs supplier; What’s the difference ?

- “No system for evaluating new suppliers of APIs was available”

- “No documentation on history of GMP-conformity of current suppliers of APIs was available“
Practical example 4: continued

- “The entry control sheet lists the items to be verified without giving any specifications for these parameters. Further, this sheet does not show the result of the entry control (acceptance or rejection of the batches) with a dated signature of an authorized person“

- “Absence of seal or broken seal not detected ”: How far do seals provide adequate proof that containers are intact?

- “Certificates of analysis were neither dated, nor signed and did not show specifications”

- “CoA did not display all tests requested by the customer “

- “There was no original CoA, only copies “
Key Point 1: How to select and follow up API suppliers?

- Regulatory environment of the manufacturer
- Existence of GMP certificates/regulatory inspections
- Audit, questionnaire, pre-sampling and pre-analysis
- Trial batches
- Contract/Technical agreement – Notification of changes
- Quality follow up indicators
  - API meets the analytical specification/trend analysis
  - Integrity of shipment
  - Deviations/complaints
- Identify the key players of the supply chain
- Need for back-up suppliers
- Regulatory: filing API manufacturers in the MA
Key Point 2: Who else is taking care of the APIs?

NB: Supplier ≠ original manufacturer

- Increasing number/complexity of links: more and more hand-offs, more storage
- Transporters
- APIs needing specific type of transportation e.g. cold temperature, secure transport (narcotics)
- Re-packer/re-labeller
- Irradiator, distributor
- Customs, storage during transport
- Virtual trader
Key Point 3: RISK: What could turn wrong ?
IMPACT: What could be the consequences ?

Anything / everything could go wrong !

- Loss of traceability
- Risk of contamination - Breach of the seals / Tampering (intentional or not, by customs or…)
- Cargo theft (high value API, psychoactive APIs, …)
- Inadequate repacking (wrong packaging material or omitting inerting gas…)
- Temperature and humidity control
  - Air route, flight connection/stop over, holding time outside the controlled temperature
  - Sea route, ground transport
  - Routes may change, delay in the transportation…
Key Point 3: RISK: What could turn wrong? IMPACT: What could be the consequences?

- When sampling is done by the manufacturer (if acceptable): route of shipment for sample and for batch may be different/ not representative
- Natural or industrial disaster or other crisis throughout the supply chain (could impact the API and the starting material for the API)
  - Hurricane, earthquake, flood
  - Nuclear accident
  - Major political crisis, war
  - Strike (dockworkers…)
  - Adulteration/falsification
- Site is found non GMP compliant by regulatory authorities (leading to shortage)
- Site is subject to sudden increase of API orders (leading to overload)
Key Point 4: MITIGATION OF RISK: Which control points and tools to mitigate the risks?

- Applying QRM to selection and follow up suppliers
- Having back up suppliers, filed in the MA
- Shorten the supply chain
- Handling of quality management, complaints, returns, recalls...
- Handling of re-packaging, re-labelling and holding of APIs
- Existence of a business continuity plan by each key player
- Having appropriate packaging materials
Key Point 4: MITIGATION OF RISK: Which control points and tools to mitigate the risks?

- Having refrigerated transport and data logger

- Checks of the API upon receipt
  - ID of the containers (name and address of original manufacturer)
  - Integrity of containers
  - ID testing of the API:
    - which sampling plan: $\sqrt{n} + 1$? all containers?
    - which method: Chemical? NIR/Raman
  - Check transportation/customs documentation
  - Authentic (original) CoA (11.40 of PIC/S GMP part 2)

⇒ Traceability - Integrity