



Statement on Good Distribution Practices
‘Guidelines on the principles of good distribution practices for active substances for medicinal products for human use’
European Commission, March 2015

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1. Introduction

This statement has been written to provide APIC interpretation about implementation of EU Good Distribution practices requirements in addition to the GMP “How To Do Document”. The statement will also provide some recommendations regarding assessments to be performed regarding management of transportation under non-controlled conditions.

1. **Distribution** – discussion on involved parties and their responsibilities in a supply chain (qualification, certification, supply chain routes knowledge, quality agreements...). This applies to procuring, importing, holding, supplying or exporting – may also involve “paper only activities” such as importing. For distribution process, the Qualified Person of the drug product manufacturer has the overall responsibility to ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP (refer to chapters 1.7.2, 1.7.3, 1.7.7 of Eudralex volume 4 Annex 16). Nevertheless, the API manufacturer is responsible to ensure that its APIs are distributed in a manner that does not negatively impact their quality and in line with the requirements described in the guideline.
2. Evaluation of actual **supply chain route** (includes storage and transport conditions of a product from its manufacturer to the final receiver). In this section, it is important to understand the physical risks of a material. A risk based approach can be used to evaluate worst case temperature excursions versus product proven stability information.



2. General

For distribution activities, it is important to clearly define roles and responsibilities of all parties involved in the distribution activity.

Such responsibilities should be clearly defined in a quality agreement or equivalent written contract.

The distribution activity of APIs includes the following stakeholders:

- API manufacturers
- Distributors, shipper, receiver or agent
- Finished drug product manufacturers (Qualified Person of the drug product manufacturer)

For each stakeholder, responsibilities shall be clearly defined. Transparency of the supply chain is a key element to fully understand the supply chain routes including associated risks and to know what is contractually agreed between the “shipper” and the “receiver”.

In the meaning of this document, the “shipper” may refer to the representative responsible for selling the API product to customer. This may be the API manufacturer, the distributor or agent. In the meaning of this document the “receiver” may be the finished drug product manufacturer or the distributor, agent, or shipper.

Note on brokers: brokering activities are not in scope of EU guideline on GDP for APIs because, as stated in the glossary section, brokering activities refer to “all activities in relation to the sale or purchase of active substances that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person”.

3. Quality Agreement arrangement

The following topics should be covered as part of the quality agreement:

Specifically for distribution within Europe, the Directive 2001/83/EC should apply for importing/exporting activities. EU based importers and exporters need to be registered as well (distribution activity).

API manufacturers with GMP license are registered for GDP as part of the GMP certificate.

- **Registration/Certification**

Stakeholders involved in the distribution of active substances must be registered according to Article 52a of Directive 2001/83/EC. In all cases, EU distributors must be registered. GDP certificate may be available for EU distributors once the Distributor is satisfactorily inspected by the competent authorities and in the cases where a GDP Certificate is issued by the EU Member State involved. Certificates should be listed in the EudraGMDP database or should be made available on request.

EU Finished drug manufacturer should provide information to the “shipper” on their GMP certificate when requested. The “shipper” has the responsibility to verify the GMP certificate of the EU Finished drug manufacturer.

The EudraGMDP database provides a source to check Manufacturing and Import authorizations (MIA’s), GMP/GDP certificates and API registrations of registered manufacturers and distributors. All EU customers should be verified for GMP/GDP registration. Refer to the GDP How To Do document for further details.



- **Knowledge of the supply chain**

The transparency regarding the supply chain is a key element to fully understand the supply chain routes including potential associated risks. Furthermore, responsibility of each party involved in the distribution activity should be clearly defined in the written agreement and understood by all parties involved within the supply chain routes. It is important to distinguish between manufacturing and distribution supply chain traceability (see figure 1). Manufacturing supply chain traceability refers to all manufacturers involved in the supply chain of a finished product or API and may go back to manufacturers of the API starting materials. Distribution supply chain traceability however includes the distributors, involved in the distribution activities between the manufacturing steps described in the “manufacturing supply chain traceability” starting from the API

The following questions may be answered to fully understand the supply chain routes:

- Who is responsible for the supply chain for a certain step in the distribution process? (supply chain owner, contracting/qualifying a certain supply chain step)
- What are the specific roles determined as part of the contract (e.g. Incoterm* conditions as an example)?
- Who is dealing with whom?
- From whom are we buying ?
- To whom are we selling?
- Who contracts the distributor to further distribute the API?

Supply chain complexity and associated risks should be considered and documented in a risk assessment. Sequential supply chain issue management such as, but not limited to, temperature excursions, damages management, intermediate storage activities need to be identified and responsibilities assigned. All parties involved within the supply chain need to be considered as part of the risk assessment (refer to the Inco* terms and arrangements) and should work with QA representatives to perform the risk assessment based on product stability data. The QP of the drug product manufacturer should ensure oversight for the presence and adequacy of the risk assessments. The oversight can either be audit based or through direct involvement.

The supply chain owner may be any party involved in the distribution activity (see diagram below) (e.g. QP of the drug product manufacturer, QA/QP of API manufacturer and/or QA of the distributor company depending on the supply chain). It is important to always refer to what has been agreed in the purchasing order, contract or equivalent document.

*** Note on Incoterm:** Incoterm conditions refer to commercial responsibilities and are significant related to responsibility for the API distribution. There are several forms of Incoterm conditions. Such information may be useful to consider as part of the supply chain assessment. Written agreements must be approved and must clearly represent the actual state of responsibilities over the supply chain as defined in Incoterm conditions. QP of drug product manufacturer must have full oversight of the supply chain and agree on responsibilities for distribution of APIs. For additional information on Incoterms, refer to ICC website (International Chamber of Commerce).



- **Qualification process**

Qualification process including subcontracting activities applies to all parties involved in the distribution activity as illustrated below:

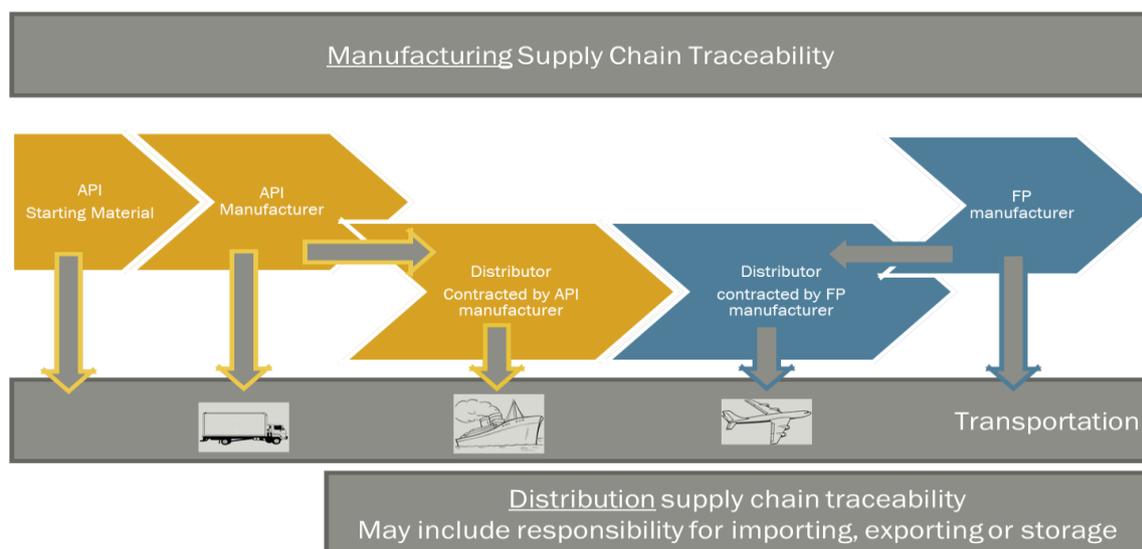


Figure 1 : Supply Chain Traceability

Depending on supply chain owner, roles and responsibilities may vary. The qualification process will apply to each relevant party responsible for the specific supply chain step.

The Quality Agreements should cover all aspects of the quality management system applicable to the distribution step and reflect the actual state of responsibilities over the supply chain as agreed following Incoterm conditions. Refer to section Knowledge of the supply chain and to the GDP How-To-Do document for further details.

Based on service provider criticality and risk assessment, periodic on site or remote audit may be decided upon to assess parties involved in the supply chain and to maintain the qualification status. For further guidance on supplier/service provider audit and risk assessment refer to APIC “How-To-Do” document on interpretation of the ICHQ7 guide. It is recommended that the GDP site audit be performed at the same time of the GMP site audit to avoid duplication and to optimize time. The frequency of the audits should be defined in the Quality Agreement.



4. Product supportive data

Product stability study data is key to justify the impact on product quality.

As stated in EU guidelines on principles of GDP for API, section 6.14 *“Active substances should be transported in accordance with the conditions specified by the manufacturer and in a manner that does not adversely affect their quality.”*

The API manufacturer is responsible to provide the supply chain owner and customer with “product temperature ranges” for which it is demonstrated the product remains stable over time. Such data may be consolidated by stability and/or forced degradation studies.

The supply chain owner should be able to understand risks within the existing supply chain routes and has the responsibility to verify that the conditions match the “product temperature range”. If the data do not match, then the supply chain owner is responsible to put actions in place to ensure the product quality will be maintained all along the product shelf-life.

In cases of excursions of temperature conditions or damage to the API packaging system, ultimate responsibility regarding **product quality assessment remains with the API manufacturer based on input data of involved supply chain party, unless otherwise defined in a quality agreement (aligned with supply agreement)**. A quality defects escalation process should be established between all relevant stakeholders involved in the distribution process. There should be an escalation process in place between supply chain owner/Finished Product manufacturer and API manufacturer.

5. Risk assessment temperature conditions for supply chain route

In this document, the transport conditions will only refer to the temperature conditions.

Although it is recognized that sensitivity to humidity and /or light are also important aspects of transportation conditions, the risk of product deterioration as a result of high humidity or light exposure is considered low because packaging is developed with the intent to protect product during storage and distribution.

For most materials, high temperature is considered more critical than low temperature stress. However, low temperature stress may need to be evaluated (e.g. Freeze/thaw cycles/precipitation...).

The risk assessment should provide the answer on the required means to ensure the "correct range of temperature" during the transportation route to avoid impact on product quality. For example, when air-land route is used, means such as passive cooling (e.g. gel packs) or other means able to mitigate the outside environment conditions could be used so the API would be "temperature controlled" in part of the route (truck) and mitigated in other parts (air/loading/unloading).



Proposal in the schematic below focusses on how to perform a risk assessment for the supply chain route and to determine the appropriate shipping conditions.

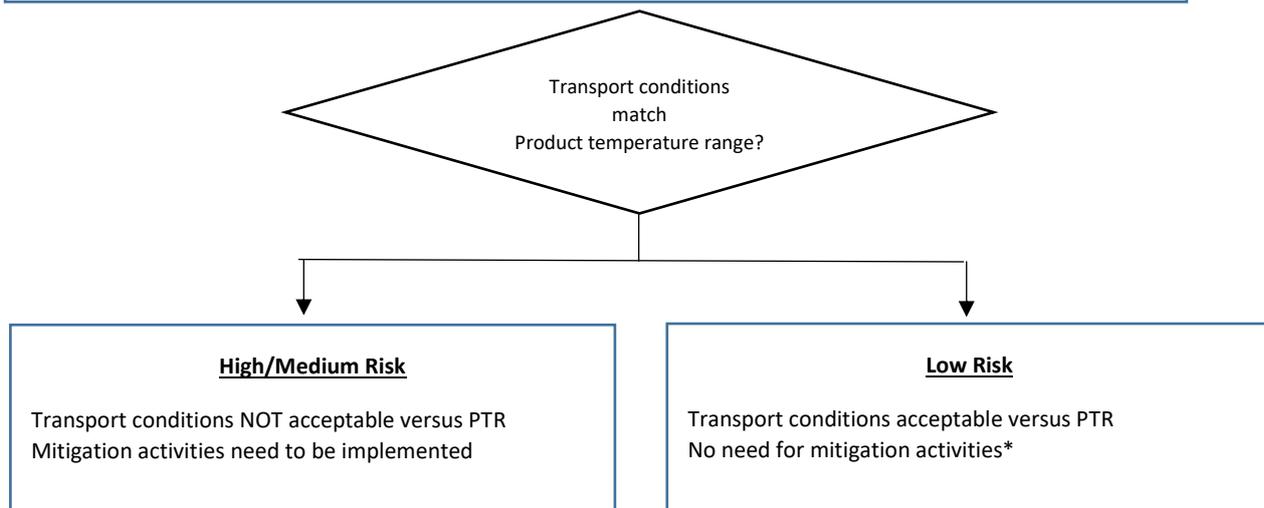
1. Identification of the product supply chain routes
(to where, to whom, who, how long?)

2. Risk assessment of the supply chain route
(what are the worst case transportation conditions?)

The assessment can be based on temperature mapping of the supply chain route and/or evaluation of climatic zones passed in the supply chain route. The assessment should include the means of transportation (truck, ship, ...) as well as transfer points. Temperature mapping should be a 'worst case representation' compared to temperature excursions that the product will effectively experience during transport.

3. Define a product temperature range (PTR)

Product temperature range is based on product stability studies, product stress testing data.



High/Medium Risk

Transport conditions NOT acceptable versus PTR
Mitigation activities need to be implemented

Low Risk

Transport conditions acceptable versus PTR
No need for mitigation activities*

Determine actions to ensure product safety/stability

Examples of possible mitigating actions:

- Actual shipment validation (to verify assumptions on temperature mapping)
- Controlled/monitored shipment using data logger*
- Optimize packaging set up
- Review product shelf life

4. Compilation of supportive data
(data loggers, product stability data, ...)

5. Periodic review
(to confirm supportive data of risk assessment)



***Note on data logger:**

Instead of putting data logger on every shipment for medium/high risks, it is acceptable to perform transportation verification using data loggers at a defined frequency based on a risk assessment.

During periodic review, it should be demonstrated that the transportation conditions remain within the validated conditions for a specific geographical area. At this stage worst case, in term of environmental conditions (e.g. warmest and coldest period), should be considered.

In the cases that extremes of temperature are recorded outside of the validated temperature range for transport, a deviation investigation is recommended to assess the potential impact on product quality. The use of mean kinetic temperature can be used to investigate the potential impact on the product quality but is deemed less suitable in case of extreme temperature variations.

6. Stability model recommendations

To determine the “product temperature range” representing transportation conditions, stress study models should be developed to demonstrate that the product remains stable over time.

Such studies should reflect the conditions applied on the product during transportation.

Typical studies may include but are not limited to:

- Put the API under stress testing conditions (e.g. highest/lowest temperature)
- Define period of time that needs to be simulated following actual conditions (e.g. 1-2 months)
- Stress studies on samples reaching the end of normal stability period could also be an option.

After performing the stress study, it is important to verify whether a new trend is created or not on product quality attributes. To do so, the product should be placed, at least, under long term stability study conditions (as per ICHQ1AR2) and should cover the retest period of the product to demonstrate that the product shelf life is not impacted by transportation conditions. It may be acceptable after a period of for example 1 year to stop the stability study if it has been demonstrated that no trend is created, such decision being supported by a risk assessment. If a new trend is created or if there is a doubt regarding the stability of the product over the time, then stability study should be extended to cover the entire product shelf-life and analysis should be performed to verify potential impact on the shelf-life of the API.

If transportation conditions have a potential impact on product quality following risk-based assessment of stability data, then actions should be taken commensurate to the risk. Typical actions may include (but are not limited to) requirements to transport the product under controlled and monitored temperature conditions.

If transportation conditions have no potential impact on the product quality following risk-based assessment of stability data, the product temperature range is determined hence no extra study will be needed except re-qualification on a predefined frequency to verify the product temperature range remains acceptable.



7. Definition

“Product temperature range”: Temperature range that an API may encounter during normal transportation conditions and for which the stability of the product has been demonstrated and proven. Stress data or forced degradation studies can be an input to define « proven temperature ranges ».

Distribution of APIs: All activities consisting of procuring, importing, holding, supplying or exporting of active substances, apart from brokering.

Supply chain owner: the one responsible for operating/managing the supply chain step(s)

8. References

- “GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE”
European Commission, March 2015
- APIC How To Do document on EU Good Distribution Practices
- ICH guideline on Stability Testing of New drug substances and Products Q1AR2
06 February 2003
- Eudralex Volume 4 Annex 16: Certification by a Qualified Person and Batch Release
- APIC How To Do document on interpretation of the ICHQ7 Guide version 09 August 2016



Attachment 1: Example of distribution Supply Chain Traceability Statement

Company name and address	Role /activity	Comments Supply agreement, Incoterm, registration Eudra GMDP
Supply chain owner	<input type="checkbox"/> Specify	
Manufacturer Name Address City Postcode Country	<input type="checkbox"/> Manufacturing, labeling, Packaging <input type="checkbox"/> Procurement from... <input type="checkbox"/> Supply to... <input type="checkbox"/> Import from... to.... <input type="checkbox"/> Export from ... to <input type="checkbox"/> Transport from ... to ... (specify specific conditions....) <input type="checkbox"/> Other activities (e.g. micronisation, repack,...)	
Distributor X Name Address City Postcode Country	<input type="checkbox"/> Storing <input type="checkbox"/> Procurement from... <input type="checkbox"/> Supply to... <input type="checkbox"/> Import from... to.... <input type="checkbox"/> Export from ... to <input type="checkbox"/> Transport from ... to ... (specify specific conditions....)	
Customer (e.g. MAH, QP manufacturing site) Name Address City Postcode Country	<input type="checkbox"/> Storing <input type="checkbox"/> Procurement from... <input type="checkbox"/> Supply to... <input type="checkbox"/> Import from... to.... <input type="checkbox"/> Export from ... to <input type="checkbox"/> Transport from ... to ... (specify specific conditions....)	

Approved by :