



Statement on Good distribution practices

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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 “How To Do Document”. This 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 doesn't negatively impact their quality and in line with the requirements described in this 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 → product proven stability information versus worst case temperature excursions evaluated in a risk assessment.



2. General

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

Such responsibilities must 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
- Finished drug product manufacturers (Qualified Person of the drug product manufacturer)

For each, applicable responsibility shall be clearly defined. Transparency of the supply chain will be a key element. Indeed, it is essential 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:

This is applicable to distribution within Europe. For importing/exporting activities the Directive 2001/83/EC shall apply. EU based importers and exporters need to be certified as well (distribution activity).

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

- **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 are normally 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 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 shall be verified for GMP/GDP registrations status. Refer to the 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.

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?
- Whom are we buying from?
- Whom are we selling to?
- Who orders the distributor to further distribute the API?

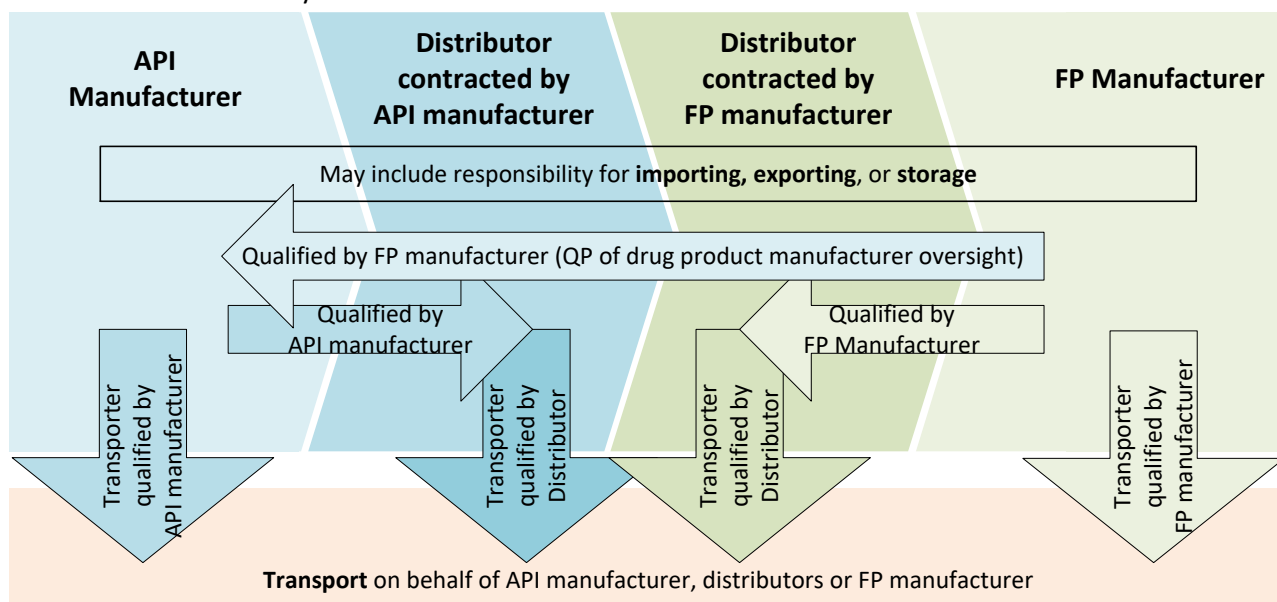
Supply chain complexity and associated risks should be considered and approved by the supply chain owner. When the QP of the drug product manufacturer is the supply chain owner, the QP is responsible to approve the risk assessment (refer to the INCO* terms and arrangements). Sequential supply chain issue 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. As an example, the Supply chain owner and QA representatives should work together to perform a risk assessment based on product stability data. The QP of the drug product manufacturer shall be involved to ensure the risk assessment has been performed. This can be verified during site audit to the API manufacturer if the API manufacturer is the supply chain owner.

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 for 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.



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 must 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 How To Do document for further details.

Periodic audits to the sites shall be in place to assess parties involved in the supply chain and to maintain the qualification status. Based on service provider criticality following the activities covered, on site audit or remote audit may be decided. This should be based on service provider risk assessment. 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 optimise time. The frequency of the audits should be defined in the Quality Agreement.



4. Product supportive data

Product stability study data are 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 customer with “product temperature ranges” that demonstrates 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 remains with the API manufacturer, unless otherwise defined in a quality 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. Product Supply Chain routes assessment - temperature conditions

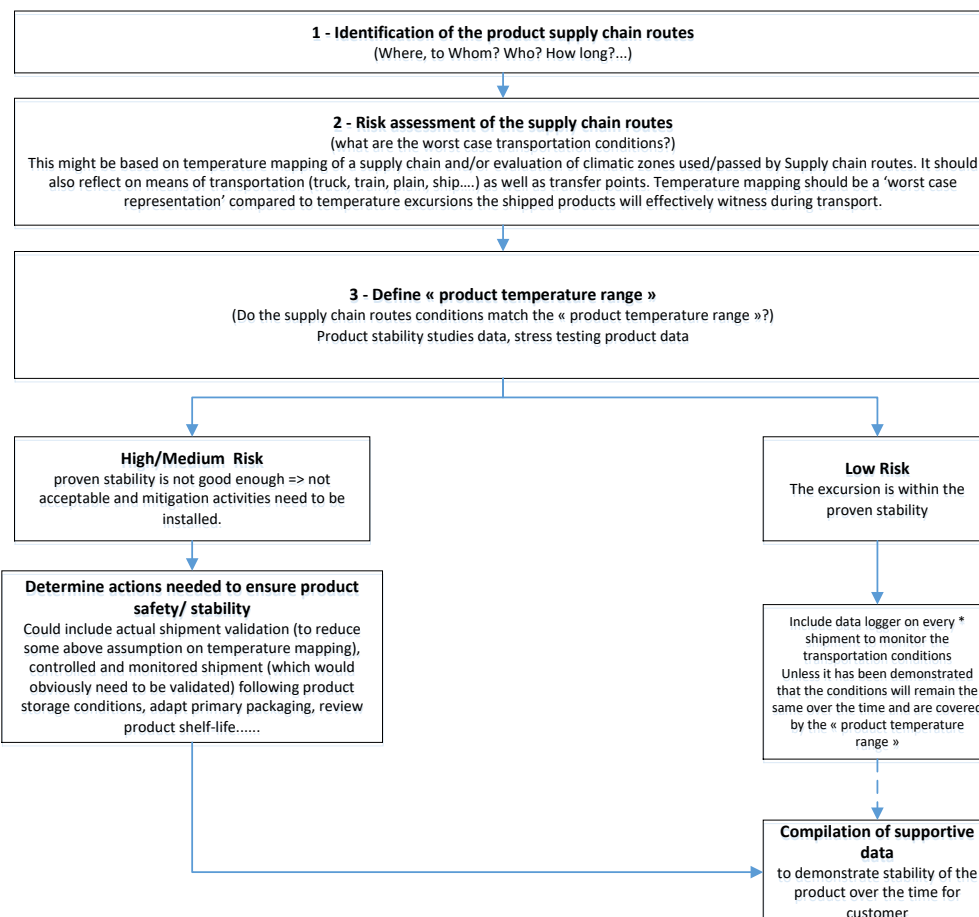
In this document, the transport conditions will only refer to the temperature conditions.

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 will usually protect product during distribution.

For most materials, high temperature is considered more critical than low temperature stress. However, this might 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. i.e. when air-land route is used, means such as passive cooling (i.e. gel packs) or any 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).

The following drawing is a proposal on what to focus on to justify product impact assessment during the supply chain and to determine shipping conditions:



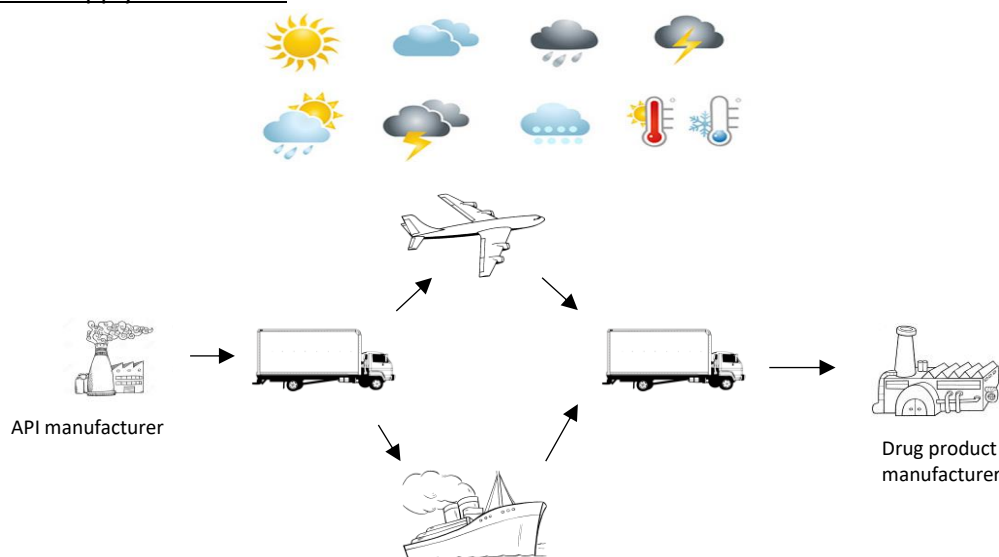
Note on data logger: Depending on the type of product shipped, there should be a decision made on case by case and based on product stability regarding check time for data logger (period of time when decision is taken to use data logger) if not put on every shipment. For low risk products (e.g. products with proven stability over extreme climatic conditions) use of data loggers on every shipment is not considered necessary.

In all cases, it is considered acceptable to perform transportation verification using data loggers at a defined frequency, such decision being supported by a risk assessment. The risk assessment should be based on stress study testing conditions and stability of the product after transportation. From this risk assessment, it may be decided not to put data logger on every shipment considering that product stability is strong enough and not affected by the transportation conditions. In such periodic verifications, worst case in term of environmental conditions (e.g. warmest and coldest period) should be considered. It is also important at this stage to demonstrate that the transportation conditions remain always within the validated conditions for a specific geographical area.



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.

Example of supply chain route:



6. Stability model recommendations

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

Such studies shall be product and transportations conditions based. Indeed, the studies shall reflect the conditions applied on the product during transportation.

Typical study may include but is not limited to:

- Put the product under stress testing conditions (e.g. highest/lowest temperature)
- Define period of time that needs to be simulated following actual conditions (e.g. 1 month, 2 months...)
- End of shelf life studies 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 shall 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 minimum 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 must be extended to cover the entire product shelf-life and analysis shall be performed to verify potential impact on the product shelf-life.

If transportation conditions have an impact on product stability, then actions must be taken to prevent that 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 impact on the product stability, thus the product temperature range is determined and 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 covers 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 active substances: All activities consisting of procuring, importing, holding, supplying or exporting of active substances, apart from brokering.

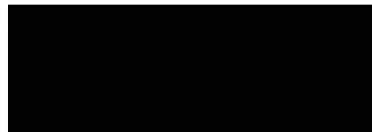
Supply chain owner: the one responsible for operating/managing the supply chain step(s)

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 Supply Chain Traceability Statement (1/6)



TO WHOM IT MAY CONCERN

Global Product Documentation



phone
fax

Date
October 5, 2015



Supply chain traceability of Active Pharmaceutical Ingredients.

1. Manufacturing

The API, [redacted] is manufactured at the site mentioned below:

Name and Addresses of
the API Manufacturing
Site



We, [redacted], hold CEP [redacted] for this product.

The starting material for the synthesis of [redacted] is:

Name of Starting
Material



We hereby declare that this starting material is only supplied from qualified suppliers, submitted to regular audits¹.

2. Other parties involved

There are no other parties involved in manufacturing process or analyses.

¹ This disclosure is in line with the requirements described in "Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template", EMA/196292/2014, 21st May 2014.

© [redacted]
The present confirmation is only valid for the ingredient supplied to customer by [redacted]. However, nothing contained herein can be construed to imply any representation or warranty regarding customer's product containing [redacted]'s ingredient.

This document contains confidential information, and should only be used in the context of the Good Manufacturing Practice requirements for Drug Products (EUDRALEX Volume 4, Chapter 5, para 5.29). All other uses would require prior written approval from [redacted].





Attachment 1: Example of Supply Chain Traceability Statement (2/6)

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Supply chain traceability of Active Pharmaceutical Ingredients.

3. Warehousing, transport

After the manufacturing, the API is transported to our [redacted] Global Distribution Center in [redacted]:

Name of Transporter from Manufacturing Site to Global Distribution Center

[redacted]

Mode of Transport

Sealed 45fr container on short sea

Name and Addresses of the [redacted] Global Distribution Center

[redacted]

API Importer & Distributor Registration Number (under Directive 2011/62/EU)

[redacted]

From the Global Distribution Center, the API is delivered to customer:

From Global Distribution Center to customers: Name of Lead Logistics Provider.

[redacted]

Mode of Transport

May vary depending on destination. For most in-land European destination, trailer on road.

We trust that these assurances address your concerns. Should you have further questions, please contact our sales office.

[redacted]

© [redacted]



Attachment 1: Example of Supply Chain Traceability Statement (3/6)

1. In this section, we declare all sites involved in manufacturing from first use of registered starting materials to final packaged good. Manufacturing would involve all steps necessary to generate the API (synthesis, fermentation, purification, formulation...), packaging, testing, release. Starting material is declared (we already disclose this in document called 'manufacturing principle').

We do not disclose suppliers of starting materials, except when they are covered by a CEP. We add the footnote to justify the non-disclosure, as we often get questions/ push-back.

TO WHOM IT MAY CONCERN

[Redacted]

Global Product Documentation

[Redacted]

phone [Redacted]

fax [Redacted]

Date
October 5, 2015

[Redacted]

Supply chain traceability of Active Pharmaceutical Ingredients.

1. Manufacturing

The API, [Redacted] is manufactured at the site mentioned below:

Name and Addresses of the API Manufacturing Site [Redacted]

We, [Redacted], hold CEP [Redacted] for this product.

The starting material for the synthesis of [Redacted] is:

Name of Starting Material [Redacted]

We hereby declare that this starting material is only supplied from qualified suppliers, submitted to regular audits¹.

2. Other parties involved

There are no other parties involved in manufacturing process or analyses.

¹ This disclosure is in line with the requirements described in "Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template", EMA/196292/2014, 21st May 2014.

The present confirmation is only valid for the ingredient supplied to customer by [Redacted]. However, nothing contained herein can be construed to imply any representation or warranty regarding customer's product containing [Redacted]'s ingredient. This document contains confidential information, and should only be used in the context of the Good Manufacturing Practice requirements for Drug Products (EUDRALEX Volume 4, Chapter 5, para 5.29). All other uses would require prior written approval from [Redacted].

Disclaimer, to specify scope of the provided info.

Here we would list other parties involved if necessary (i.e. third parties involved in analytics, tool manufacturers...)



Attachment 1: Example of Supply Chain Traceability Statement (4/6)

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05.10.2015, Page 2 of 2
Supply chain traceability of Active Pharmaceutical Ingredients.

3. Warehousing, transport

After the manufacturing, the API is transported to our [redacted] Global Distribution Center in [redacted]:

Name of Transporter from Manufacturing Site to Global Distribution Center	[redacted]
Mode of Transport	Sealed 45fr container on short sea
Name and Addresses of the [redacted] Global Distribution Center	[redacted]
API Importer & Distributor Registration Number (under Directive 2011/62/EU)	[redacted]

From the Global Distribution Center, the API is delivered to customer:

From Global Distribution Center to customers: Name of Lead Logistics Provider.	[redacted]
Mode of Transport	May vary depending on destination. For most in-land European destination, trailer on road.

We trust that these assurances address your concerns. Should you have further questions, please contact our sales office.

[redacted]

© [redacted]

Concerning transportation, we do not provide information concerning delivery of starting material, as it is outside of scope of GMP (production of active substance start at the point at which «active substance materials» are entered into the process, Eudralex Vol4 part II).



Attachment 1: Example of Supply Chain Traceability Statement (5/6)

BACKGROUND ON RECORDS REQUIRED FOR SUPPLY CHAIN TRACEABILITY

EUDRALEX Vol 4 Chapt 5	
5.29	Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance. The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.
Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template (May 2014)	
	For chemically synthesised active substances, it is acknowledged that details of the suppliers of designated starting materials may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer's quality system for starting materials.
Questions and answers: Good manufacturing practice	
	3. What are the expectations with regard to documentation and verification of the supply chain for active substances (ref. Paragraph 5.29, Chapter 5 EU GMP Guide)? H+V August 2015 The supply chain for each active substance must be established back to the manufacture of the active substance starting materials. This should be documented and must be kept current. The risks associated with this supply chain should be formally documented. Control of each incoming consignment of active substance should include verification that it has been received from the approved supplier and approved manufacturer. The entire supply chain should be verified for a supplied batch periodically to establish a documented trail for the batch back to the manufacturer(s) of the active substance starting materials. The frequency of this verification should be based on risk.
Eudralex Vol 4 Annex 16 (revision)	
1.7.2	The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the QP. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process.



Attachment 1: Example of Supply Chain Traceability Statement (6/6)

<u>CMDh Questions and Answers, Applications for MA (CMDh/268/2012, Rev.5, Jan 2016) (revision)</u>	
	<p>Question 16 What level of details should be provided for active substance manufacturers on application forms for new marketing authorisations, variations and renewals?</p> <p>Answer: Names and addresses of all sites involved in the manufacture of the active substance from the first use of the designated active substance starting materials should be provided. This includes intermediate manufacturers, quality control sites and in-process testing sites and is irrespective of the means by which the data requirements for the active substance are met – by either EDQM Certificate of Suitability (CEP), Active Substance Master File (ASMF) or full details in the dossier. For CEPs, also sites not openly declared on the CEP should be provided. Any sites not applied for are considered to be non-approved. Subsequent changes to the information provided would also trigger a need for a variation application.</p>