Shipment under Quarantine

Document valid from:	**14.02.2024**	
Document number:	**I-SMI.TI.26e**	**Version 1.0**
Classification:	**Public**	
Replaced document:	**--**	dated: --
Root SMI documents:	**--**	
Referenced QMI documents:	**--**	

Approval	Date:	Signature:
Author:	16.01.2024	Christian Schärer
Technical verification:	19.01.2024	Federico Cimini
Formal verification (Release VS-QMI):	14.02.2024	Michelle Scheidegger

Index

1 Purpose and scope

During recent inspections, it was observed that active substances, intermediates or even finished products are shipped from a manufacturing site to another or even to distribution partners abroad, under quarantine whilst quality control tests and batch record review are ongoing and batch certification by the manufacturer have not yet been performed, although in principle products should not be sold or supplied before a Qualified Person has certified the batch.

This document aims to clarify in which situations a shipment under quarantine would be acceptable to inspectors. It covers different situations of shipment of active substances and intermediate drug products, as well as finished drug products.

Not within the scope of this document is the situation when some regulatory flexibility is allowed to address exceptional circumstances (e.g., due to shortage situations, pandemics, etc.) where a shipment before batch certification is necessary to accelerate the availability of critical products (e.g. Covid vaccines).

2 Basics

- Eudralex Vol. 4 Part 1 and 2
- PIC/S PE 009

The following paragraphs are of main interest in the context of shipment under quarantine

Part I (for intermediate and finished drug products)

- *1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:*
- *(xv) Medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;*
- *1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that:*
- *(vii) No batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations in accordance with annex 16;*
- *5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.*
- *5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.*
- *5.64 The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 6 (Quality Control).*
- *Ch. 6 Principle*

- *This chapter should be read in conjunction with all relevant sections of the GMP guide Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.*

Part II (for active substances)

- *2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).*
- *6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.*
- *6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).*
- *10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.*

Annex 16 (for active substances as well as intermediate and finished drug products)

- *1.1. Each batch of finished product must be certified by a QP within the EU before being released for sale or supply in the EU or for export. Certification can only be performed by a QP of the manufacturer and/or importer which are described in the MA.*
- *4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by a QP as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.*
- *4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.*

3 Definitions and abbreviations

SuQ	Shipment under Quarantine

4 Interpretation

When investigating the different examples where a shipment under quarantine was observed during inspections, it became clear that different situations might need to be distinguished. The following different situations were identified and assessed in this document:

1. Transfer of manufactured goods from one site to another site (for further manufacturing/storage) of the same company. Both sites belong to the same legal entity and are covered under the same manufacturing authorization and should be under the same quality system.
2. Transfer of manufactured goods from a manufacturing site to another site (for further manufacturing/storage) whereas both sites are belonging to the same corporate group (e.g. located in another country). Although belonging to the same company network, the two sites represent separate legal entities and are working under separate manufacturing authorizations. Although there are some common corporate quality guidelines, the quality systems of the two companies is not the same.
3. Transfer of manufactured goods as contract manufacturer back to the contract giver.
4. Transfer of manufactured finished products from a manufacturing site to a central storage/distribution hub (for global distribution).
5. Transfer of manufactured finished products to clients/local distributors.

As the relevant current GMP requirements for shipment are not identical between GMP Part I and Part II, there is a need to assess for all five situations, if a shipment under quarantine is acceptable for
- Active substances (API)
- Intermediate/Bulk drug products
- Finished drug products

There are several factors that may influence the company's decision to ship the products under quarantine, e.g.
- Acceleration of manufacturing processes within the company's global network
- Limited storage capacity
- Use of outsourced global storage and distribution hubs
- Compensation of longer shipping times when changing from air- to groundfreight, e.g. for cost reduction reasons or in order to improve CO_2 foot print

4.1 General GMP considerations regarding SuQ

- The general principle of GMP is that manufactured goods should be held in quarantine until their release. This is underlined by the multiple repetitions of this principle in the GMP Guide. In general, shipments under quarantine are therefore not fully in compliance with GMP and should therefore not be the standard procedure that is applied unless appropriate safeguard measures are in place.
- The manufactured goods should remain under the responsibility of the manufacturer and should remain physically at the manufacturer's place until release. This is only achievable if the physical handling and the release decision is under the same responsibility and quality system of the manufacturer. Any transfer involving third parties (e.g. logistics) represents an additional risk that needs mitigation measures.

- The mentioned GMP principle applies especially to products falling under Part I. Shipment of finished drug products under quarantine before the batch is certified by the QP is not acceptable as a standard procedure. Only justified exemptions (e.g. justified by the labile nature of the product, such as some radiopharmaceuticals or cell therapy products) may be assessed on a case-by-case basis. Only in the event that very robust safeguard measures have been taken it is conceivable that a quarantine shipment could take place outside of an exceptional situation.
- Eudralex Vol. 4 Part 2 offers some flexibility allowing shipment of active substances under quarantine if special safeguards are in place.
- An assessment of the GMP compliance of SuQ in the different settings is necessary. The following table summarises the assessment of Swissmedic and the regional inspectorates for the cases considered most frequent. For alternative cases, the principles expressed in the table can be used as decision support.

	Case	Product category	SuQ	*Ref.*
1	Transfer of manufactured goods from one site to another site (for further manufacturing/storage) of the same company. Both sites belong to the same legal entity and are covered under the same manufacturing authorization and should be under the same quality system.	API	SuQ is acceptable, as a transfer within a company as a normal process. The manufactured goods must be under the common quality system of the company and the status of the material needs to be under control at any time.	*Part II 2.1, 10.20*
		Intermediate/ Bulk Finished products	SuQ is acceptable, as a transfer within a company as a normal process. The manufactured goods must be under the common quality system of the company and the status of the material needs to be under control at any time.	*Part I 1.8*
2	Transfer of manufactured goods from a manufacturing site to another site (for further manufacturing/storage) whereas the two sites belong to the same corporate group but are different legal entities. The two sites are working under separate manufacturing authorizations and therefore under a separate quality system although there is a common Quality system on corporate level. The two sites may be located in different countries.	API	SuQ is acceptable, - if sufficient control is available by the two quality units and appropriate controls and documentation are in place ensuring that the products are not used for further manufacturing until products are released - if – in case of exported products - the competent authority of the receiving country has agreed to this procedure	*Part II 10.20*
		Intermediate/ Bulk	SuQ is acceptable, - if sufficient control is available by the two quality units and appropriate controls and documentation are in place ensuring that the products are not used for further manufacturing until products are released - if – in case of exported products - the competent authority of the receiving country has agreed to this procedure	*A16 4.1, 4.2*
		Finished products	SuQ is not acceptable in general, but only in exceptional situations and if the company has documented evidence of a written approval by the competent authority. SuQ is acceptable if a robust system is in place between the local manufacturing site and the corporate structure in charge of the certification process of the goods to prevent premature release. In any case, shipment under quarantine of finished products to a central distribution hub belonging to the same corporate group is only acceptable if this hub is located in a country that applies EU GDP rules.	*Part I 5.63, A16 1.1, 4.1, 4.2*

	Case	Product category	SuQ	*Ref.*
3	Transfer of manufactured goods as contract manufacturer back to the contract giver. The two sites are working under separate manufacturing authorizations and separate quality systems.	API	SuQ is acceptable, - if sufficient control is available by the two quality units and appropriate controls and documentation are in place. ensuring that the products are not used or shipped for further manufacturing until products are released - if - in case of exported products - the competent authority of the receiving country has agreed to this procedure - Transfer of manufactured goods from a contract manufacturer to a third party for further manufacturing which is not the contract giver is only acceptable if agreed among all three partners.	*Part II* *10.20*
		Intermediate/ Bulk Finished products	SuQ is acceptable - if sufficient control is available by the two quality units and appropriate controls and documentation are in place. ensuring that the products are not used or shipped for further manufacturing until products are released - if - in case of exported products - the competent authority of the receiving country has agreed to this procedure - Transfer of manufactured goods from a contract manufacturer to a third party for further manufacturing which is not the contract giver is only acceptable if agreed among all three partners.	*Part I* *5.63* *A16* *4.1, 4.2*
4	Transfer of manufactured goods to a central distribution hub under third party control	API	SuQ is acceptable, - if sufficient control is available by the two quality units and appropriate controls and documentation are in place ensuring that the products remain under quarantine and are not used or shipped for further manufacturing until products are released - if this central distribution hub is located in a country that applies EU GDP rules as an EU country or in a formalised manner through a bilateral agreement with the EU. - if - in case of exported products - the competent authority of the receiving country has agreed to this procedure	*Part II* *10.20*

	Case	Product category	SuQ	*Ref.*
		Intermediate/ Bulk	SuQ is acceptable, - if sufficient control is available by the two quality units and appropriate controls and documentation are in place ensuring that the products remain under quarantine and are not used for further manufacturing until products are released - if this central distribution hub is located in a country that applies EU GDP rules as an EU country or in a formalised manner through a bilateral agreement with the EU. - if - in case of exported products - the competent authority of the receiving country has agreed to this procedure	*Part I 5.63, A16 4.1, 4.2*
		Finished products	SuQ is only acceptable if the technical release/certification process of the goods remains under the full control of the company, e.g. via a validated software interface with the hub's ERP. In any case, shipment under quarantine to a central distribution hub is only acceptable if this hub is located in a country that applies EU GDP rules as an EU country or in a formalised manner through a bilateral agreement with the EU.	*Part I 5.63, A16 4.1, 4.2*
5	Transfer of manufactured (finished) products to clients/local distributors.	API	SuQ is not acceptable in general, but only in exceptional situations and if the company has documented evidence of a written approval by the competent authority.	*Part II 6.70, 6.71*
		Intermediate/ Bulk Finished products	SuQ is not acceptable in general, but only in exceptional situations and if the company has documented evidence of a written approval by the competent authority.	*Part I 5.63, A16 1.1, 4.1, 4.2*

5 Changes to the previous version

- None (first version)

6 Annexes

- None