QUARANTÄNE VERSAND

REGINE SCHWARZ
08.06.2016, WIEN

AGENDA

- Evaluierungsergebnisse relevanter Regularien
- Interpretationen aus dem Internet
- SOP für Versand unter Quarantäne

ANNEX 16

4. THE RELEASE OF A BATCH

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.

ANNEX 16

4.3 The **steps necessary to notify QP certification** to the site where the transfer to saleable stock is to take place should be defined within a **technical agreement**. Such notification by a QP to the site should be **formal and unambiguous** and should be subject to the requirements of Chapter 4 of EudraLex, Volume 4, Part I.

ICH Q7A & EU GMP PART II

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).

10.20 Distribution Procedures

- **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.

INTERPRETATION - Q7 Q&As

- transport situations that are not considered distribution ... **physical movement** (transfer but not release) of quarantined material to another unit. This unit can be on the **same site, different site (within the same company**), or a contract manufacturer...
- goal ... is to allow **transportation and testing in parallel**
- Material ... is **not to be used for further processing** until all testing and quality review is complete and the material is released by the quality unit

INTERPRETATION - Q7 Q&As

- ... situations where a company is shipping **APIs or intermediates** from one unit to another and has both the need to expedite the shipping and the material management system in place to **prevent use of the material before full release**
  (e.g. extraordinary supply chain requirement(s) such as short shelf-life), and materials with a lengthy timeframe for required test(s) (e.g., some microbiological tests, etc.)
- ... **appropriate oversight** ... including a **written agreement** ... and appropriate ongoing controls, a **contract manufacturer may be considered a 'unit under the company's control'.** There is **a joint responsibility by both parties** to clearly justify and document the need to transfer the unreleased intermediate or API, and to ensure appropriate control is maintained to prevent use before full release.

ANNEX 13
RELEASE AND SHIPPING

38.

Release of investigational medicinal products (see paragraph 43) should not occur until after the Qualified Person has certified that the requirements of Article 13.3 of Directive 2001/20/EC have been met

43.

Investigational medicinal products should **remain under the control of the sponsor** until after **completion of** a two-step procedure: **certification** by the Qualified Person; **and release** by the sponsor for use in a clinical trial following fulfillment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC.

GCP - SHIPMENT UNDER QUARANTINE

Interpretation → Interfaces to GLP and GCP

Particularly in early phases of development, when no long-term stability data is yet available for the clinical samples, shipment under quarantine is sometimes required (... before all test results are available)...

… quite questionable considering the requirements of Annex 13, and **must be agreed** in individual cases **with the authorities of the countries involved**

Paragraph 43 of Annex 13

- "Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step release procedure"

... This means that **shipment cannot take place until it has been approved by the sponsor**. If samples are to be shipped under quarantine, the sponsor (if necessary via the monitor) must **ensure** that the investigational medicinal **products are not used in the Contract Research Organisation** until formal release has been granted.

If the **products cannot be released** in the end, it must be ensured that the test formulations are **returned or destroyed** on site

INTERPRETATION ZUSAMMENFASSUNG

Die Weitergabe unter Quarantäne wird akzeptiert, wenn

- dies unter der **Kontrolle der Qualitätsabteilung** des Herstellers des Wirkstoffs oder des Zwischenprodukts geschieht,
- **nur für den Transport** an dritte Parteien mit Zustimmung der Qualitätsabteilungen beider Parteien
- Kontrollen sind in der **Qualitätsvereinbarung** beschrieben
- **formelles Dokument** und ein **formelles Kontrollsystem** der dritten Partei gewährleistet die erforderliche Kontrolle des unter Quarantäne gestellten Materials
- für an **Subunternehmer vergebene Aktivitäten** sollten die **formellen Qualitätsvereinbarungen** dieses Szenario abdecken.

SOP FÜR VERSAND UNTER QUARANTÄNE

- Prozess festlegen
  - Organisationseinheiten involviert
- begründete Ausnahmefälle?
  - Drug shortage, short shelf life of material, …
- Ausnahmefälle für welche Prozessstufen?
- Voraussetzungen definieren
  - Regelung im Quality Agreement
  - schriftliche Anforderung mit Begründung
  - Prüfung ob Charge für Versand unter Quarantäne geeignet ist
- Prüfungen und Genehmigung
  - Prüfungen durch QA Funktion
  - Status von Batch Record Review
  - Status von Abweichungen hinsichtlich der Qualität, Wirksamkeit und Sicherheit
  - keine bestätigten OOS-Ergebnisse
  - Genehmigung durch QP
- Dokumentation
  - Formular
  - Bestätigung des Anforderers das die Charge nicht „*for further processing*“ eingesetzt wird
  - Kennzeichnung bei Versand

WEITERE REGULARIEN

- Suchwörter
  - Conditional release, (quarantine) shipment / transport, shipment under conditions, final release, distribution
- Keine Ergebnisse
  - CFR
  - USP Good storage and shipping practices
  - PIC/S 008

REFERENZEN

- EudraLex – Vol.4, Annex 13, Annex 16
- 21 CFR § 211
- ICH Q7A
- USP Good storage and shipping practices
- PIC/S 008