ASMF: GMP PERSPECTIVE AND REGULATORY COMPLIANCE FROM STARTING MATERIALS TO API

API Traceability, Supply Chain and QP Declaration : which impact for the Drug Product Manufacturer

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- *Normative e linee guida*
- *Qualifica, verifiche e controlli sulla Supply Chain*
- *“Written Confirmation”*
- *“QP Declaration”*

NORMATIVE E LINEE GUIDA – PRODUZIONE API

- EU GMP, parte II (ICH Q7)
- WHO Technical Report Series, No. 957, 2010, annex 2 "GOOD MANUFACTURING PRACTICES FOR ACTIVE SUBSTANCES"

NORMATIVE E LINEE GUIDA – GDP PER API

- EU GMP parte II, capitoli 10.2 e 17
- Good Distribution Practice of active substances for medicinal products for human use (EC Guideline of 19 March 2015)
- PIC/S Questions & Answers document regarding Distribution Activities for Active Pharmaceutical Ingredients (APIs) (PS/INF 20/2011 24 March 2011)
- WHO Technical Report Series, No. 996, 2016, annex 6 "GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS"

NORMATIVE E LINEE GUIDA – IMPORTAZIONE DI API

- Directive 2011/62/EU
- D.Lgs. n. 17 del 19 Febbraio 2014 (Modifica D.Lgs. 219/2006)
- Aggiornamento alla guida all'implementazione del D.Lgs. n. 17 del 19 Febbraio 2014, che modifica il D.Lgs. 219/2006, in materia di produzione, importazione e controllo di sostanze attive e di eccipienti
- Avviso agli importatori di sostanze attive titolari di autorizzazione alla produzione di medicinali e titolari di AIC (15/12/2015)
- Nuova modulistica per istanze importazione sostanze attive da parte di titolari di autorizzazione produzione medicinali e precisazioni per titolari AIC (01/03/2016)
- Nuova modulistica per le istanze di importazione di sostanze attive da parte di titolari di AIC (28/02/2018)

NORMATIVE E LINEE GUIDA – "WRITTEN CONFIRMATION"

- **Template** for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC Version 2.0 (January 2013)
- **Question & Answers** on importation of active substances for medicinal products for human use (EC, version 4.1)

NORMATIVE E LINEE GUIDA – "QP DECLARATION"

- **Template** for the qualified person's (QP) declaration concerning good manufacturing practice compliance of active substance manufacture "The QP declaration template" (EMA/334808/2014)
- **Guidance** for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template" (EMA/196292/2014)
- **Questions and answers** on the template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration tem (EMA/CHMP/CVMP/QWP/696305/2010)

Produttore di medicinali : qualifica, verifiche e controlli sulla supply chain

- Produzione di API (inclusa la produzione degli starting materials)
- Distribuzione di API (trasporto, stoccaggio intermedio)
- Importazione di API (da Paesi extra EU)
- Produzione di medicinali (controlli e verifiche sulla supply chain degli API)

Produzione di API

- **Qualificazione del Produttore di API**
  - Raccolta documentazione CMC (CoA, certificati di purezza, ecc.)
  - Audit GMP
  - Test su campioni (corrispondenza alle specifiche, test di produzione, ecc.)
  - Studi di stabilità sul medicinale
  - Contratto di fornitura / Quality Assurance Agreement
  - Registrazione nel CTD

Produzione di API

- **Monitoraggio del Produttore di API**
  - Aggiornamento documentazione CMC
  - Audit di follow up o ad hoc
  - Gestione modifiche e variazioni (anche al CTD)
  - Valutazione performance (affidabilità consegne, gestione lotti fuori specifica, risposte a reclami, collaborazione nelle indagin su problemi di qualità, ecc.)
  - Monitoraggio notifiche di non compliance alle GMP da parte di Autorità (AIFA, EMA, EDQM, FDA)

Distribuzione di API

- **Qualificazione del Distributore di API**
  - Verifica e raccolta documentazione autorizzativa
  - Audit GMP/GDP
  - Contratto di fornitura / Quality Assurance Agreement
- Qualificazione del Trasportatore di API : come Distributore
- Qualificazione di *Agents, Brokers e Traders* : come Distributore

Importazione di API

- **Autorizzazione AIFA (se diretta)**
- **Qualificazione dell'Importatore di API**
  - Verifica e raccolta documentazione autorizzativa
  - Verifica "Written Confirmation" (se applicabile)
  - Audit GMP/GDP
  - Contratto di fornitura / Quality Assurance Agreement

PRODUTTORE DI MEDICINALI : QUALIFICA, VERIFICHE E CONTROLLI SULLA SUPPLY CHAIN

Produzione di medicinali

- **Conoscenza , documentazione e aggiornamento della supply chain**
  - Documento descrittivo della supply chain (parte del sistema qualità)
  - Gestione delle variazioni della supply chain
  - Mantenimento della Regulatory Compliance (aggiornamento CTD e QP Declaration)
  - Verifica della Supply Chain in occasione di ogni consegna

Produzione di medicinali

- **Verifica della Supply Chain in occasione di ogni consegna**
  - Documentazione di trasporto
  - Certificato di analisi del Produttore
  - Verifica "Written Confirmation" (se applicabile)

"Written Confirmation" vs "QP Declaration"

- WC : documento di carattere "GMP"
- QPD : documento di carattere "Regolatorio"

“Written Confirmation”

Directive 2011/62/EU, art. 46b2

- **Active substances shall only be imported if the following conditions are fulfilled:**
  - a) the active substances have been **manufactured** in accordance with standards of **good manufacturing practice at least equivalent to those laid down by the Union** … (ICH Q7)

“Written Confirmation”

Directive 2011/62/EU, art. 46b2

- b) the active substances are **accompanied by a written confirmation from the competent authority** of the exporting third country of the following:

“Written Confirmation”

Directive 2011/62/EU, art. 46b2

- (i) the **standards of good manufacturing practice** applicable to the plant manufacturing the exported active substance are at least **equivalent to those laid down by the Union** ……..;
- (ii) the **manufacturing plant** concerned is subject to **regular, strict and transparent controls** and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the Union; and
- (iii) in the event of **findings relating to noncompliance**, **information** on such findings is supplied by the exporting third country **to the Union without any delay**.

“Written Confirmation”

- Template, version 2.0 (January 2013)
- EC Question & Answers (4.1, 2013)

“Written Confirmation”

Q&A – EC – 2013

12. QUESTION: WHO CHECKS THAT THE IMPORTED ACTIVE SUBSTANCE IS ACCOMPANIED BY THE WRITTEN CONFIRMATION?

Answer:

This should be checked by the **receiving manufacturer of the finished medicinal product.** It may also be checked by the importer of the active substance upon its importation.

It may be verified :

- by the relevant authority upon importation;
- and/or - in the context of an inspection of the importer of the active substance,
- and/or - **in the context of an inspection of the manufacturer of the medicinal product that uses the imported active substance.**

“Written Confirmation”

Q&A – EC – 2013

26. QUESTION: ARE THERE EXCEPTIONS FROM THE REQUIREMENT OF A WRITTEN CONFIRMATION?

Answer:

The Commission publishes a **list of countries** which, following their request, have been assessed and are considered as having **equivalent rules for good manufacturing practices to those in the EU**. Active substances manufactured in these countries **do not require a written confirmation**.

- Switzerland, Australia, USA, Japan, Israel, Brasil.

“QP Declaration”

- Marketing authorisations require a **QP declaration** to confirm that the **active substance has been manufactured in accordance with Good Manufacturing Practice** (GMP) for medicinal products for human and veterinary use, Part II: Basic Requirements for Active Substances used as Starting Materials .

“QP Declaration”

- A QP declaration is required to be **submitted with all applications for new marketing authorisations, renewals and submissions of relevant quality variations**, concerning changes (addition or replacement) to the manufacturer of a starting material and / or to the registered manufacturer(s) of the active substance, finished product or batch importation/certification sites.

“QP Declaration”

- the QP declaration should be **based upon an audit of the active substance manufacturers** . It is established good practice that the audit should be conducted at the manufacturing site i.e. an **on-site audit**.
- Audits should be **by or on behalf of the MIAH**, by suitably trained and experienced person(s), who may be a third party contractor .
- The audit **cannot be replaced by GMP certificates** from a relevant competent authority

“QP Declaration”

- Part A: Concerned active substance manufacturing sites
- Part B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies
- Part C: Basis of the declaration
- Part D: QP declaration
- Part E: Name and signature of QP responsible for this declaration

“QP Declaration”

- **PART C: Basis of the declaration**
  - An **on-site audit** is expected
  - In **exceptional circumstances** (*no on site audit available*), the QP declaration should be supported by:
  - (a) the **justification** for assessment of GMP compliance in lieu of on-site audit;
  - (b) a listing of the **documents forming the basis of the off-site audit**, for example - questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier, and risk analysis.

“QP Declaration”

- **PART C: Basis of the declaration**
  - Section (ii) **sites audited, auditors and date of audit** :
    - Audits of each site for GMP compliance should be undertaken at regular intervals, **normally within three years**. Justification should be provided if the date since the last audit exceeds this period.
  - Section (iii) **supplementary information** :
    - Supplementary information that may be attached to the QP declaration to support a **risk-based approach** by the manufacturer in establishing priorities for its own **audit programme**.

Grazie !

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