PHARMAprocess

Innovation Forum in Pharmaceutical Process

GDP. What is the impact to the API manufacturers.

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1. INTRODUCTION

Supply chain traceability from beginning to the end is required

GUARANTEE APIs QUALITY

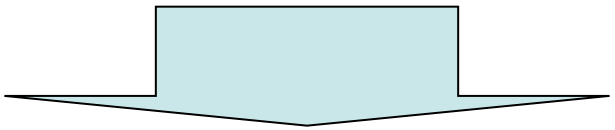
2015/C 95/01 EC – GDPs APIs – 19th March 2015 (21st September 2015)

EU-GMPs Part I – Chapter 5 section 5.29 – 1st March 2015

EU-GMPs Part II – Chapters 10 and 17 – 1st September 2014

RD 782/2013 – Spanish legislation – 11th October 2013

EU-GMPs Part I – Chapter 1 section 1.10 – 31st January 2013



ALIGN THE REQUIREMENTS OF THE HEALTH AUTHORITIES WITH THE APIs MANUFACTURERS, DISTRIBUTORS AND FDF MANUFACTURERS

2. LEGISLATION

EU-GMP Part I Chapter 5

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**

AUDITS should be carried out at the **MANUFACTURERS** and **DISTRIBUTORS** of active substances to confirm that they **COMPLY** with the relevant good manufacturing practice and **good distribution practice requirements.**

The **supply chain and traceability records** for each active substance should be **AVAILABLE** and be retained

2. LEGISLATION

Questions & Answers EMA:

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.

2. LEGISLATION

EU-GMP Part I Chapter 1

PRODUCT QUALITY REVIEW (PQR)

(i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of **supply chain traceability** of active substances.

2. LEGISLATION

RD 782/2013 Article 24:

1. Los laboratorios farmacéuticos fabricantes o importadores tienen la obligación de:

   a) Documentar la **cadena de suministro** de cada material de partida.

   b) Asegurar el cumplimiento de las normas de correcta fabricación por parte de los fabricantes y de las **buenas prácticas de distribución** por parte de distribuidores de los principios activos. (…) se deberán AUDITAR A INTERVALOS REGULARES, a los fabricantes y distribuidores de principios activos, para confirmar que cumplen los requisitos de las normas de correcta fabricación y buenas prácticas de distribución de principios activos. La frecuencia de las auditorías será **AL MENOS DE UNA VEZ CADA TRES AÑOS, SALVO QUE SE JUSTIFIQUE UN PERIODO MAYOR EN BASE A UN ANÁLISIS DE RIESGOS.**

API manufacturer

DIRECT SUPPLY

transport

FDF manufacturer

NON DIRECT SUPPLY

transport

Carriers / warehouses

transport

3. FDF MANUFACTURERS: HOW TO KNOW AND VERIFY THE SUPPLY CHAIN OF APIs?

- ✓ SUPPLY CHAIN TRACEABILITY STATEMENT FOR EACH API and MANUFACTURER
- ✓ QUALITY AGREEMENTS (including supply chain traceability responsibilities)
- ✓ AUDITS TO API MANUFACTURERS (transport/warehouses/etc.)
- ✓ AUDITS TO API DISTRIBUTORS (transport/warehouses/etc.)

…. in order to have a good knowledge of the supply chain

3.1 SUPPLY CHAIN TRACEABILITY STATEMENT FOR EACH API and MANUFACTURER

- Documented supply chain for each API and manufacturer (See example: STATEMENT)
- Revision of the supply chain by the FDF manufacturer
- Risk analysis of the supply chain for each API and manufacturer in order to:
    - Evaluate the risk
    - Reduce the risk (decrease the probability of occurrence, increase detectability). Residual risk (Acceptable?)
    - Implement corrective actions / TA / measures to control and monitor

3.2 QUALITY AGREEMENTS

In case of Direct Supply:

Quality agreement between API manufacturer and FDF manufacturer

In case of Non direct supply:

Quality agreement between API manufacturer – API distributor – FDF manufacturer (third parties agreement possible)

IN BOTH CASES: SUPPLY CHAIN RESPONSIBILITIES SHOULD BE PROPERLY DEFINED

3.3 AUDITS TO API MANUFACTURERS

Audit approach based on EU-GMP part II and GDP for APIs

Audits should be undertaken at intervals defined by the quality risk management process **to ensure the maintenance of standards and continued use of the approved supply chain.**

During the audit is important to verify

- APIs supply chain
- Control that the manufacturer has on the agents (audits, TA)
- API stability studies (ex.: in case of temperature excursions during transport)

3.3 AUDITS TO API MANUFACTURERS

CONCLUSIONS

In General:

- *Control of temperature in API manufacturer facilities* ***GOOD***
- *Self inspections include warehouse facilities and temperature control* ***GOOD***
- Supply chain control (risk analysis): control of the outsourced agents **NEEDS IMPROVEMENT**
- Quality Agreements with the different outsourced agents **NEEDS IMPROVEMENT**
- GDP implementation **NEEDS IMPROVEMENT** (ex: continuous personnel training in GDP)
- Qualification of the supply chain agents **NEEDS IMPROVEMENT**

3.4 AUDITS TO API DISTRIBUTORS

Audit approach (based on GDP for APIs, internal quality requirements of FDF manufacturer and activities performed):

- Personnel
- Documentation system
- Premises and equipment
- Operations: orders, receipt, storage, deliveries to customers, transfer of information
- Returns, complaints and recalls
- Self inspections
- Supply chain control (risk management) and agreements
- Quality certifications (Generally ISO9001)
- Computerized systems

3.4 AUDITS TO API DISTRIBUTORS

CONCLUSIONS

- **Good knowledge of the medicinal products distribution sector**
- **Big companies have invested in improving facilities and trucks**
- **ISO 9001 certified**
- Supply chain control (risk analysis): control of the agents outsourced **NEEDS IMPROVEMENT**
- Quality Agreements with the different agents outsourced **NEEDS IMPROVEMENT**
- GDP implementation **NEEDS IMPROVEMENT (ex: deviations, CAPA and change control reports, continuous personnel training in GDP)**

4. MAIN DIFFICULTIES FOUND BY THE FDF MANUFACTURER

- Difficulties in getting the supply chain documented

- Continuous changes of the agents involved in the supply chain

- Difficulties in being informed of the supply chain changes (mainly when different agents are involved, non direct purchase from the API manufacturer)

… difficult to know the temperature conditions of the API during the supply chain when there are long distances between the API manufacturer and FDF manufacturer and different agents involved


THANK
YOU !

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