PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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Questions & Answers document regarding Distribution Activities for Active Pharmaceutical Ingredients (APIs)

by the PIC/S Expert Circle on APIs

Introduction

This list of Questions and Answers were agreed by inspectors of the PIC/S Expert Circle of APIs at a meeting in Dublin, Ireland in May 2010. The document is intended to provide guidance to inspectors when inspecting areas relating to two topics: (a) Supply Chain & Distribution and (b) Repackaging & Relabelling operations. References to the PIC/S Guide to GMP Part II are provided to answers, where appropriate.

Q1. Should records other than GMP records (e.g. financial records) be examined during inspections to verify the sources and parties involved in the sale and distribution of APIs?

A1. In regular circumstances, the documentation detailed in section 17.20 should be adequate in order to verify traceability of APIs distributed. However, this list is not limitative and other documents such as financial records may also be requested for further demonstration of traceability.

Q2. Who is considered to be the original manufacturer if an API undergoes further processing (e.g. micronisation, sterilization & repackaging) after its last manufacturing step?

A2. The manufacturer producing the API, as described in the registration documents, applications or equivalent, is considered as the original manufacturer. All other subsequent intervening parties performing further physical processing of APIs (e.g. micronisation, milling, granulation, irradiation, coating and repackaging) are not considered as the original manufacturer but should be described in the registration document, be known by the Marketing Authorisation holder and the finished product manufacturer. It is imperative that all manufacturers involved in the production chain are known.

Q3. Could distributors of APIs sub-contract production steps (e.g. micronisation, sterilisation)?

A3. Yes, as far as such production steps are described in the registration documents, applications or equivalent and the appropriate quality contracts identifying the different parties (distributor, manufacturer and/or laboratory) are established according to the requirements of section 16.

Q4. How does the finished product manufacturer assure its knowledge about and the integrity of the whole API supply chain?

A4. The whole API supply chain should be established, known and documented by the finished product manufacturer in collaboration with the API manufacturer as part of its supplier selection and approval process. The supply chain should be reviewed periodically to ensure its validity including by means of audits when appropriate.

Q5. What kind of information is requested about transport conditions of APIs? Does the shipping process need to be validated?

A5. The level of information required depends upon the stability of the API considered. Communication of the transport and storage conditions by the API manufacturer is established according to the requirements of section 10.2. In the case of an API requiring specific storage conditions (e.g. below 8°C), proof should be available that the required storage and shipping conditions are maintained throughout the transport chain from the API manufacturer to the finished product manufacturer. This may be achieved through validation and verification (e.g. continuous temperature/humidity monitoring) where required. The API manufacturer has responsibility for ensuring that transport and storage conditions are stated on the product label (section 10.22) and that all parties involved in the distribution process are informed of those requirements (section 10.23)

Q6. Which aspects should be focused on during inspections of brokers / traders?

A6. Inspections of parties negotiating independently and on behalf of another entity without physical handling of APIs or intermediates should focus on quality management, traceability aspects and transfer of information as detailed in section 17.

Q7. Section 11.40 of GMP states that 'authentic Certificates of Analysis (CoA) should be issued for each batch of intermediate or API on request'.

(a) What could be considered as an authentic CoA?
(b) How can its authenticity be guaranteed?
(c) Should an authentic CoA be provided systematically for each customer?
(d) Can it be issued more than once?

A7.

(a) An authentic CoA of a batch is a record of analytical results from the API manufacturer, dated and signed manually or electronically by the authorized person, meeting all requirements of section 11.4.

(b) The verification of the authenticity of the CoA could be achieved by contacting the API manufacturer using its contact details present on the CoA.

(c) Yes, a copy of the authentic CoA should be provided to each customer at least.

(d) Yes, several authentic CoAs can be issued e.g. in the case of the distribution of one batch to several customers.

Q8. There is no definition included in PIC/S GMP guidelines regarding relabeling and repackaging activities. What is PIC/S APIs experts' view on that matter?

A8. Relabelling of containers is the placing of additional labels onto containers which does not impact, obliterate or destroy the manufacturer's original label, in order to maintain traceability of the supply chain. Any act of relabeling that impacts upon the manufacturer's original label and hence traceability, may be considered as adulteration or an attempt of falsification. A repackaging operation consists of replacing any material intended to protect an API or intermediate during transport and storage (e.g. primary packaging, secondary packaging, and desiccant, etc.).

Q9. Which aspects should be focused on during inspections of repackagers / relabellers?

A9. Repackaging and relabeling activities are considered as manufacturing operations. Therefore, full compliance with all relevant sections of the PIC/S GMP guide PE 009 (Part II) is required as mentioned in the PIC/S aide-memoire PI 030.

Q10. What level of quality testing is expected from relabellers?

A10. For relabellers, no analytical testing is expected. However, a robust quality system should be in place in order to prevent mix-ups or loss of identity, purity or traceability as per section 17.40. Full recording of relabeling operations should be maintained.

Q11. Is it acceptable to hide the origin of an API after repackaging / relabelling operations?

A11. No. (see Question 8 also). According to sections 17.60 and 17.61, the name of the original API manufacturer and batch number should be provided. Furthermore, Certificate of Analysis from the original API manufacturer mentioning its contact details should be transferred to the customer as stated in sections 11.43 and 11.44.

Q12. What measures should be implemented at a repackaging site where different batches are blended.?

A12. Blending operations should only be performed in compliance with the relevant requirements of Part II of the PIC/S GMP guide and in particular those detailed in sections 8.4, 8.51 and 8.52. The specifications should be at least equivalent to those established by the original manufacturer and suitable for the intended use of the material. Appropriate testing of the blended batch should be performed to determine conformance to the specifications. Blending operations should be validated.

Q13. Should stability studies be performed on repackaged APIs?

A13. Stability studies should be performed unless justified and documented. Stability studies may not be required if documented evidence is available demonstrating that the repackaging material is equivalent to or more protective than the original packaging material - reference section 17.50.