



APIC QUICK GUIDE FOR API SOURCING

Final Version: 30 September 2008

APIs from Legitimate and Reliable Sources

1. Introduction

Counterfeit and sub-standard APIs are increasingly present. Not only are they a fact of non-compliance but also they form a serious and increasing risk for patient safety. Various initiatives have been taken such as the founding of the FDA Counterfeit Drug Task Force, the European Commission's current "Public consultation in preparation of a legal proposal to combat counterfeit medicines for human use" and the WHO Program "IMPACT" (International Medical Products Anti-Counterfeiting Taskforce).

This document focuses on the interaction between the API manufacturer and the medicinal product manufacturer and provides possible measures that may be taken by both partners in order to ensure only non-rogue APIs are used in the manufacture of medicinal products. The proposed measures are considered as elements out of a whole puzzle. A risk-based approach should be applied to determine the necessity and value of the individual proposals, alone or in combination.

The document does not address in detail the vendor qualification process as it is taken for granted that APIs are only purchased from suppliers that have been thoroughly evaluated and approved by Quality Assurance in line with GMP requirements.

2. Supply Chain: Agents, Brokers, Distributors, Repackers, Relabelers

As a general principle, the shorter the supply chain, the more secure it will be. This is reflected in the EU GMP Guidelines, Part 1 (5.26) specifying that starting materials (APIs, excipients) should be purchased, where possible, *directly* from the producer.

In addition to the length of the supply chain, any changes on the original container – e.g. by repackaging, relabeling – should be considered as an additional risk for alteration and should therefore, whenever possible, be avoided.

There is no doubt that the entire supply chain needs to be assessed from a quality perspective, covered by an effective supplier qualification program and the same principles as described in the following sections for the direct supply from API manufacturer to drug product manufacturer should be applied.

This already starts at the point of selecting the contractor for transportation of the API (see also ICH Q7, 10.23).

3. On Site Visits / Audits

3.1. Visits

A thorough knowledge of the supplier is a key element. Therefore, a close and stable relationship between the manufacturer of the API and the drug product manufacturer should be achieved by using various means of contact. A regular exchange between

sourcing- and purchasing people and the supplier contributes to strengthening this relationship, especially if the contact also includes regular visits on site. Site visits should not be restricted to the manufacturing site alone; intermediaries in the supply chain should be covered as well. It should be ensured that representatives of the purchasing department have a good GMP- and regulatory awareness and technical understanding so that these visits are as beneficial as possible, also in relation to compliance.

3.2. Audits

An audit is considered the most effective way of verifying concrete and compliant manufacturing incl. distribution of APIs. However, apart from the fact that an audit is very time-consuming it only provides a snapshot of the situation and there is no 100% guarantee that evidence for any occurring counterfeiting activities may be identified. Nonetheless, there are various elements in a quality audit that may increase that probability and that respectively may confirm the reliability of the manufacturer.

3.2.1 General

Whenever possible, the audit should be executed when an actual production campaign is ongoing.

Requests for changing the agenda at short notice during the audit, e.g. revisiting areas on another time or day, may be a useful approach to confirm the consistency of operations on site.

3.2.2 Warehouse

The walk-through in the warehouse supports the verification of the materials management capability with respect to claimed annual production of the API and storage capacity.

Checking for the presence of intermediates or APIs in the warehouse that have been purchased and could be subject for relabeling or of APIs intended to undergo a reprocessing may lead to the identification of different sources of materials than claimed. The list of approved vendors should also be reviewed for this purpose.

The review of the materials management system and material movements (booking in/out) of concerned API starting materials, intermediates and the final API is another possible source of information in the warehouse. However, confidentiality with respect to other customers' names needs to be respected.

3.2.3 Production

The walk-through in production should cover the verification of the necessary equipment and necessary utilities by cross-checking with the production instruction and/or process flow chart.

3.2.4 Document Review

The review of master production instructions as well as analytical methods and specifications for raw materials, intermediates and the API as well as of executed documents/raw data and cross-checks with the regulatory document (e.g. DMF, CMC section, CEP dossier) is an important element in verifying regulatory compliance.

One can also verify the availability of production records and/or analytical raw data as well as retained samples (where applicable) of raw material, intermediates and API batches for specific batches that were either identified from the review of the stock cards/materials management system, product quality review or from supplied batches.

The timely and sequential correlation of equipment use logbooks in production and QC laboratory, production batch records (incl. electronic raw data), cleaning records and analytical raw data (incl. date/time on equipment print-outs such as balances, chromatographic systems etc.) is a good indicator for on site production.

The review of the documentation related to seals (specifications – testing/approval according to specifications – reconciliation documentation – authorized persons identified and documented...) may be added.

A spot wise review of analytical raw data from stability studies (not only the summary table) as well as of the logbook of the stability chambers (e.g. date of sample in/out) and the check for physical availability of the stability samples should be included.

The adequate involvement of the drug product manufacturer in case of changes that can impact the quality and/or regulatory compliance of the API may be verified by the reviewing the history of changes and individual change request cases related to the production and testing of the API (incl. intermediates, raw materials),

4. Supporting Documentation

The availability of certain documents that are regularly available and up-dated, where applicable, may be considered as one efficient element in the continuous supplier monitoring process.

4.1 Inspections, Inspection history

As part of the initial evaluation of a potential API supplier the GMP inspection history, with respect to inspecting regulatory body, inspection date, inspected areas (as far as this information is / is made available) and the inspection results should be reviewed. A regular up-date of the inspection history as part of the supplier monitoring and re-qualification process should be performed.

On the other hand, as these inspections are not mandatory for APIs e.g. used in medicinal products for the EU, the non-availability of an inspection history may not lead to the conclusion that this API supplier is less reliable.

4.2 GMP certificates

GMP certificates of the API manufacturer, where available (see 4.1), should be provided, ideally as authentic copies.

4.3 Certificate of Analysis

A thorough review of Certificate of Analysis, against regulatory documents (e.g. DMF, CMC section, CEP dossier) and in-house specification respectively, and with respect to GMP compliance (ICH Q7, 11.14) should be performed as part of incoming release testing of APIs. Suppliers involved in counterfeiting *could* apply improper documentation practices.

In case of agents, brokers etc. being involved in the supply chain it is recommended to insist on a certificate of analysis issued by the original manufacturer of the API (see also 2.). Where a new certificate of analysis is prepared by agent, broker, distributor, there should be a reference to the name and address of the original manufacturer and a copy of the original batch Certificate should be attached, as specifically required by ICH Q7 11.43, 44

4.4 Certificate of Compliance, Compliance Commitment

A certificate of compliance issued by the API manufacturer, either as a separate document or as part of the certificate of analysis, which certifies that a specific batch has been manufactured according to ICH Q7 GMP requirements and in line with the applicable Registration Documents can provide additional assurance related to the awareness of the manufacturer on the quality and regulatory expectations of the customers.

4.5 On-going stability program

A GMP compliant manufacturer has an on-going stability program for its APIs (ICH Q7, 11.5). At least one batch of the API manufactured per year is added to the stability program and tested at least annually. A regular up-date of the program provided by the API manufacturer, not necessarily including stability data, gives additional assurance for actual and compliant systems.

4.6 Product Quality Review

The major objective of the Product Quality Review (ICH Q7, 2.5) is to evaluate the compliance status of the manufacture (process, packaging, labelling and tests) and to identify areas of improvement based on the evaluation of key data. It includes a review of critical in-process controls and critical API test results, of batches that failed to meet specification, of changes carried out, of the stability monitoring program, of quality-related returns/complaints/recalls and of the adequacy of corrective actions. Due to the comprehensive information included, the Product Quality Review provides a good overview of the manufacture of a certain API.

The document should be reviewed during an audit or as a minimum an approved executive summary should be made available by the API manufacturer.

4.7 Quality Agreement

The quality agreement as a tool to clearly define the GMP responsibilities strengthens the awareness of liabilities of both partners. The extent and level of detail of the agreement may vary and can depend on the material supplied, e.g. generic API versus exclusively synthesized API, but it should at least address

- name of the product
- mutually agreed specification (if not covered by supply agreement)
- manufacturing site
- applicable cGMP standards, e.g. ICH Q7
- compliance with the DMF or with other registration documentation
- GMP audits related to the API (e.g. 3rd party auditing)
- documents to be provided by the manufacturer, e.g. certificate of analysis, certificate of compliance, inclusion of copies of respective master documents may be addressed
- arrangements for transportation and transport packaging (see 5.), e.g. description and degree of tampering proof seal to be used, inclusion of a copy of the master drum label may be considered
- deviation handling
- handling of and response to complaints
- change management: involvement of the customer with respect to notification and approval
- list of approved signatories may be included

5 Packaging: labeling, tamper-proof sealing

If the API manufacturer provides examples/templates of master labels, which he uses to label the containers, this supports the drug product manufacturer in identifying any manipulation on the material on its way from the manufacturer to the recipient.

The use of tamper-resistant packaging closure by the manufacturer provides additional assurance that the material was not adulterated on its way from the manufacturer to the drug product manufacturer. A manufacturer-specific design of the seal is recommended to be used; the use of unique seals may be considered. The communication of the type of seal, by the manufacturer to the user, completes the information chain.

6. Material Inspection, Sampling, Analysis, Impurity Profile

At the point of receipt the first relevant action is to carefully perform the visual inspection of all the containers of the API. Attention shall be paid to the integrity and type of the sealing as well as to the special attributes added by the manufacturer (see above 4.7, 5.) such as label design, seal number and design.

The applied sampling regime related to the number of containers sampled, number of samples taken per container, analysis of individual and/or pooled samples as well as the extent of analysis, varying from identity test to full analysis may influence the probability of identifying counterfeiting, provided it may be identified by analytical means.

A risk-based approach, considering the qualification status of the supplier, may be chosen to define the extent of sampling and testing, considering the requirements for drug product manufacturers (e.g. Annex 8 to EU GMP Guidelines).

The impurity profile is normally dependent on the production process and origin of the API. The comparison of the impurity profile of a current batch with either previous batches or data provided by the manufacturer (e.g. as part of the regulatory submission) may help in order to identify changes related to modifications in the production process and may indicate whether the API might originate from a different manufacturer than the supposed one.

It is recommended to check the current (im)purity profile and compare it with former quality in regular intervals, at least once a year.

GLOSSARY

API

Active pharmaceutical ingredient (synonym: drug substance)

Counterfeit API

Active pharmaceutical ingredient for which source and/or quality are falsely represented on the label, on the certificate of analysis or otherwise

Rogue API

API that is counterfeit or severely, deliberately non-compliant.

ACKNOWLEDGEMENTS

This document was originally prepared by a group of experts within CEFIC/ APIC. We thank them for their work and efforts spent as well as for their kindly co-operation, intensive discussions and fruitful comments:

- Claudia Stampfli (Lonza)
- Stephan Rosenberger (Lonza)
- Ricardo Giralt (Boehringer-Ingelheim)
- Luisa Paulo (Hovione)
- Tony Storey (Pfizer)
- Iain Moore (Croda)
- Henri Leblanc (Rhodia)
- Rodney Horder (Abbott)
- Rainer Fendt (BASF)
- François Vandeweyer (Janssen Pharmaceutica)
- Chris Oldenhof (DSM)
- José Luis Ortega (Pharma Mar)
- Tom Buggy (DSM)