



The APIC Audit Programme Version 3, August 2010

Table of contents

- 1 General**
- 2. APIC Audit Program**
- 3 The Auditors**
 - 3.1 Educational Background and Experience**
 - 3.2 Auditor Training Courses for 'Certification'**
 - 3.2.1 Certification of Auditors
 - 3.3 Contract**
- 4 The Audit Process**
 - 4.1 Steps of the Audit Process**
 - 4.1.1 Preliminary Talks
 - 4.1.2 Preparation for the Audit
 - 4.1.3 Selection of Auditors
 - 4.1.4 Execution of the Audit
 - 4.1.5 Audit Report: Reviewing, Signing and Archiving
 - 4.1.6 Resolution of Disagreement with GMP deficiencies / Performance of Auditors
 - 4.2 Audit Follow-up**
 - 4.3 Audit Feedback**
- 5 Cost Considerations**
- 6 Relationship between APIC and the API Compliance Institute**

Annexes

- Annex 1 Contract between Auditor and the API Compliance Institute
- Annex 2 Agreement on Audit Execution between the Customer, Auditee, Auditors and API Compliance Institute
- Annex 3 APIC Auditing Guide -Secrecy Agreement for APIC Audit Programme
- Annex 4 Standardised letters relate to Shared Third Party Audits
- Annex 5 Form to request feedback on Audit / Auditor performance from Auditee.

1 General

According to the EU legislation *'the holder of a manufacturing authorization shall at least be obliged to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials'* (Directive 2001/83/EC as amended, article 46(f) for Human Medicinal Products and Directive 2001/82/EC, Article 50(f) for Veterinary Medicinal Products).

The Document entitled "Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials" (1) and the EMA Website GMP Question and Answers on audits of active substances manufacturers (<http://www.ema.eu.int/Inspections/GMPfaqAS.html>) give further guidance on what the European Authorities expect in terms of assessing the GMP status of active substance manufacturers.

An audit conducted by or done on behalf of the Manufacturing Authorisation Holder (Manuf.Auth.Holder) of their Active Pharmaceutical Ingredient (API) Manufacturers / Suppliers should be an integral part of the Supplier Qualification Procedure of the Manuf.Auth.Holder.

Audits should be performed by qualified and trained staff, the audit should be properly documented and the audit reports will be subject to inspection by the Competent Authorities during inspections of the Manuf.Auth.Holder for the Medicinal Products.

Audits should be done periodically (every 2 to 3 years) to assess the continuing GMP Compliance status of the API Manufacturer and, as necessary, the Agent, Broker, Packer, Re-Packer, Distributor or Importer of the API.

If a Third Party is involved then the Manuf.Auth.Holder as "contract giver" should follow Chapter 7 of the EU GMP Guide and evaluate the Third Party auditors / audit process as the "contract acceptor" to ensure that the audit process complies with their GMP expectations. The Manuf. Auth. Holder should ensure there is no conflict of interest between the audit process, the auditors and the Auditee.

In view of the legal background and the GMP expectation of supplier evaluation by the authorities, the Qualified Person(s) or responsible person(s) of the Manuf.Auth.Holder is responsible to assure that the APIs used in Human and Veterinary Medicinal Product Manufacture are manufactured according to the EU GMP guidelines for APIs.

Several Audit Options are acceptable to the European Authorities:

- The Customer / Supplier Audit or **Second Party Audit** that would be performed by the Qualified Auditors of the Manuf.Auth.Holder for each API Manufacturer.

The audit may also be performed by the Qualified Auditors of the Marketing Authorisation Holders, for example in the case where the Marketing Authorisation Holder is responsible for the Manufacture or Supply of the API and contracts out the manufacture of the Medicinal Product to the Manuf.Auth.Holder for the Medicinal Product). The audit report and findings should be reviewed by the Qualified Person(s) of the Manuf.Auth.Holder. In this case, the responsibilities for auditing of the API Manufacturer should be defined in the Technical Contract between the Marketing and Manufacturing Authorisation Holders.

(1) The Guidance was published in 'Compilation of Community Procedures on Inspections and Exchange of Information', <http://www.ema.eu/Inspections/GMPCompproc.html>

- A **Third Party Audit** of the API Manufacturer performed on behalf of the Qualified Person(s) or responsible person(s) of the Manuf.Auth.Holder. The Qualified Person(s) or responsible person(s) of the Manuf.Auth.Holder (Contract Giver) confirms that the Third Party Audit Process provides an effective assessment of the GMP status of the API manufacturer and that the audit is performed by independent, qualified Auditors with no conflict of interest.
- **Shared Third Party Audits** are acceptable to the European Authorities as long as the Qualified Person(s) ensures that the scope of the audit is applicable to each Medicinal Product that uses the API as Starting Material.

A Third Party Audit can either be initiated by one or more Manufacturing Authorisation Holder(s) ('called 'customer') or by the API Manufacturer / Distributor / Broker / Importer/ Packer / Re-Packer itself (called 'Auditee').

If the API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer initiates the audit, the purpose of the audit is a **self assessment** of the GMP status of the API Manufacturer.

The API manufacturers may use such audit programmes beyond the EU QP requirements as part of their own API supplier qualification management.

Guidance on Supplier Qualification and Management is given in the APIC publication

- In the opinion of the Ad Hoc GMP Inspection Services meeting of EU Inspectors organized by EMA, the Manufacturing Authorisation Holders should decide for themselves whether there are any conflict of interest issues with any Third Party Audit Option.

2 APIC Audit Program

The approach taken by many Medicinal Product Manufacturers towards this legal requirement is to perform one to one audits of their API manufacturers. However it is recognised that audits are time-consuming and expensive for both the API and Medicinal Product Manufacturer and there is potential for significant audit overload for the Pharmaceutical Industry if this is the only option used.

The aim of the APIC Audit Programme is to provide a standardised Third Party Auditing process to ensure that an effective assessment is performed of the GMP status of APIs used as Starting Materials for Medicinal Products sold within Europe and in so doing contribute to the assurance of the Quality, Safety and Efficacy of the Medicinal Products.

The API Compliance Institute as a Business Unit of Concept Heidelberg has been contracted by APIC to administer the APIC Audit Programme.

The audits within the framework of the APIC Audit Programme are conducted by APIC Certified Auditors and standardised reports with classification of findings are issued.

Third Party Audits should be initiated by the Marketing Authorisation Holder for the Medicinal product according with the European directive 2001/83/EC and its amendments where it is defined that is the responsibility of the Manuf. Auth. Holder to assure that the API is manufactured in accordance with the cGMPs in force.

In the case that several Manuf. Auth. Holders wish to cooperate on an audit of the same API Manufacturer or share an audit report the 'Third party audit' becomes a '**Shared Third Party Audit**'.

Once the initial request to arrange the audit has been made to The API Compliance Institute ,other potential customers for the 3rd Party Audit could be contacted using the Standardized letter (Annex 4) and if they wish to share in this audit, they should contact the API Compliance Institute within 1 month.

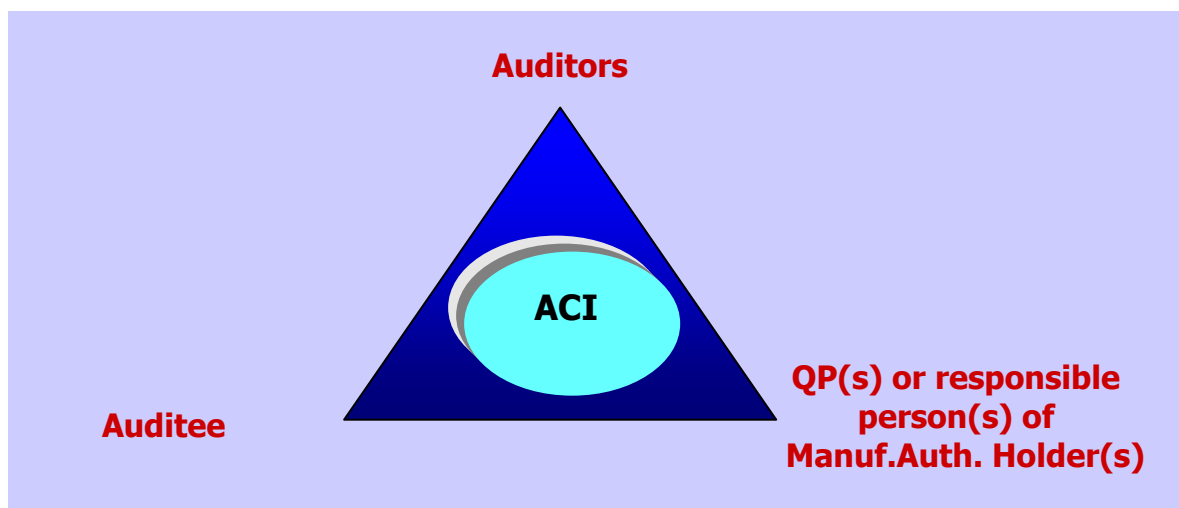
In the case that a Third Party Audit has recently been performed and the API Manufacturer is contacted by a QP or responsible person of another Manuf. Auth. Holder who is interested in assessing whether this Third Party Audit Report satisfies their requirements, the representative of the Manuf. Auth. Holder should be asked to contact the API Compliance Institute. This scheme can also be applied to non EU Manuf. Auth. Holders.

In the case that the API Manufacturer, / Distributor / Broker/ Importer / Packer / Re-Packer initiates the request for a Third Party audit of their Manufacturing Site, the audit will be for the purpose of performing a **self-assessment audit**. This will be documented in the Audit Agreement and included as a Footnote in the Audit Report.

Important:

The 'Compliance Triangle principle' (see figure 1) will be followed at all steps of the audit process to ensure that all parties involved - the 'customer', the 'Auditee', the auditors and the API Compliance Institute as the coordinator of the audit are involved in the communication processes.

Figure 1: Compliance Triangle Principle of the APIC Third Party Audit Programme



Request by the QP(s) or Responsible Person(s) of the Manufacturing Authorisation Holder(s): Third Party Audit of API Starting Material used in Medicinal Products

Request by the API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer: Self Assessment Audit of GMP status

ACI = API Compliance Institute

Auditee = API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer

QP = Qualified Person

Manuf.Auth.Holder = Manufacturing Authorisation Holder for Human or Veterinary Medicinal Products.

Participation in the APIC Audit Programme is on a voluntary basis and is not limited to members of APIC nor to a specific region of the world.

The CEFIC APIC Auditing Guide documentation

(<http://www.apic.cefic.org/pub/Auditing/Auditing%20Guide%20Final.pdf>) provides the

framework for the standardised audit programme. Trained Auditors follow the principles defined in the Auditing Guide, to ensure that a comprehensive assessment of the GMP status of each API Manufacturer or as necessary Distributor, Trader, Broker, Importer, Packager, Re-packager of the API is performed and that full documentation is available to describe the audit.

The audit report will include descriptions of all subjects covered during the audit, objective evidence for any GMP deficiencies found during the audit will be included in the report and such deficiencies will be classified by the Auditors in one of the following categories (classification rating) that are based on the definitions included in the EMA GMP Inspection Report Format

<http://www.ema.europa.eu/Inspections/GMPCompproc.html>

Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing an Active Pharmaceutical Ingredient that could be harmful to the human or veterinary patient.

Major Deficiency:

A non critical deficiency which has produced or may produce a product, which does not comply with its marketing authorization or which indicates a major deviation from EU Good Manufacturing Practice, or a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such

Other Deficiency:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

3 The Auditors

3.1 Educational Background and Experience

The Auditors should have a good educational knowledge of chemistry. Qualifications as Pharmacist, Medical Doctor, Chemical Engineer, graduate or Ph.D. in Chemistry, Biology or related fields as Agrochemistry etc., are appropriate. A good understanding of biochemistry and analytical techniques and practices is a definite advantage.

At least 5 years practical experience of GMP manufacture of Active Pharmaceutical Ingredients may also be considered as sufficient knowledge and background.

With the exception of Pharmacists whose university courses may include modules on GMP Regulations, a good knowledge of applicable regulations is usually obtained through training and experience.

3.2 Auditor Training Courses for ‘Certification’

Attendance at a specific five-day training course sponsored by APIC (two and a half days related to GMPs in API manufacture and two and a half days for training in effective auditing techniques) is a prerequisite for becoming an APIC Certified Auditor. The participant will receive a certificate of attendance for each of the two training courses.

The seminar fees will be charged directly to the Auditor or his company.

3.2.1 Certification of Auditors

In order to become an APIC Certified Auditor, the Auditor has to undergo an examination. This examination consists of 2 parts.

Part 1: The participant has to take a written exam on the contents of the GMP-compliant manufacture of APIs in accordance with ICH Q7. This written exam is created by APIC in co-operation with the API Compliance Institute. After the training course, the participant is given access to a total of 30 questions via the Internet. These have to be answered following the multiple-choice procedure. For this task, the participant has 60 minutes. He/she has passed the exam if 70% of the questions have been answered correctly. In case of failure, the exam can be repeated twice. The costs have to be borne by the participant.

Part 2: An APIC representative who is a trainer in the course and a trainer with academic education in psychology assess the auditing skills of the participants during the Training Course.

The APIC representative judges the participant's ability to conduct audits within the framework of the APIC Auditing Programme. The psychologist assesses the verbal and non-verbal communication, analyses the art of questioning and conversation techniques as well as the behaviour in conflict situations. These ratings are put down on a form including a statement whether or not the trainee auditor should become an APIC Certified Auditor and the form is archived at the API Compliance Institute together with the record of performance in the examination (Part 1) .

The records are kept as long as the Auditor maintains his/her certification. Afterwards the records are archived for another 7 years.

Auditors who have successfully passed Part 1 and Part 2 will then become APIC Certified Auditors. The Certificate is valid for three years (see 2.3).

Those Auditors who would like to become active within the framework of the APIC Auditing Programme have to indicate this together with their proof of educational qualification and experience (see point 2.1.) on the application form for the training course.

The API Compliance Institute keeps a register of all APIC Certified Auditors.

The Auditor's certification can be extended for subsequent three year periods provided he/she has attended at least two recognised training courses / conferences on current GMP Topics and has satisfactorily performed at least three audits during the current period of certification.

If either of these conditions are not met, the Auditor's name will be withdrawn from the register of APIC Certified Auditors.

All current APIC Certified Auditors will be required to take the examination test at the time of their next Re-Certification.

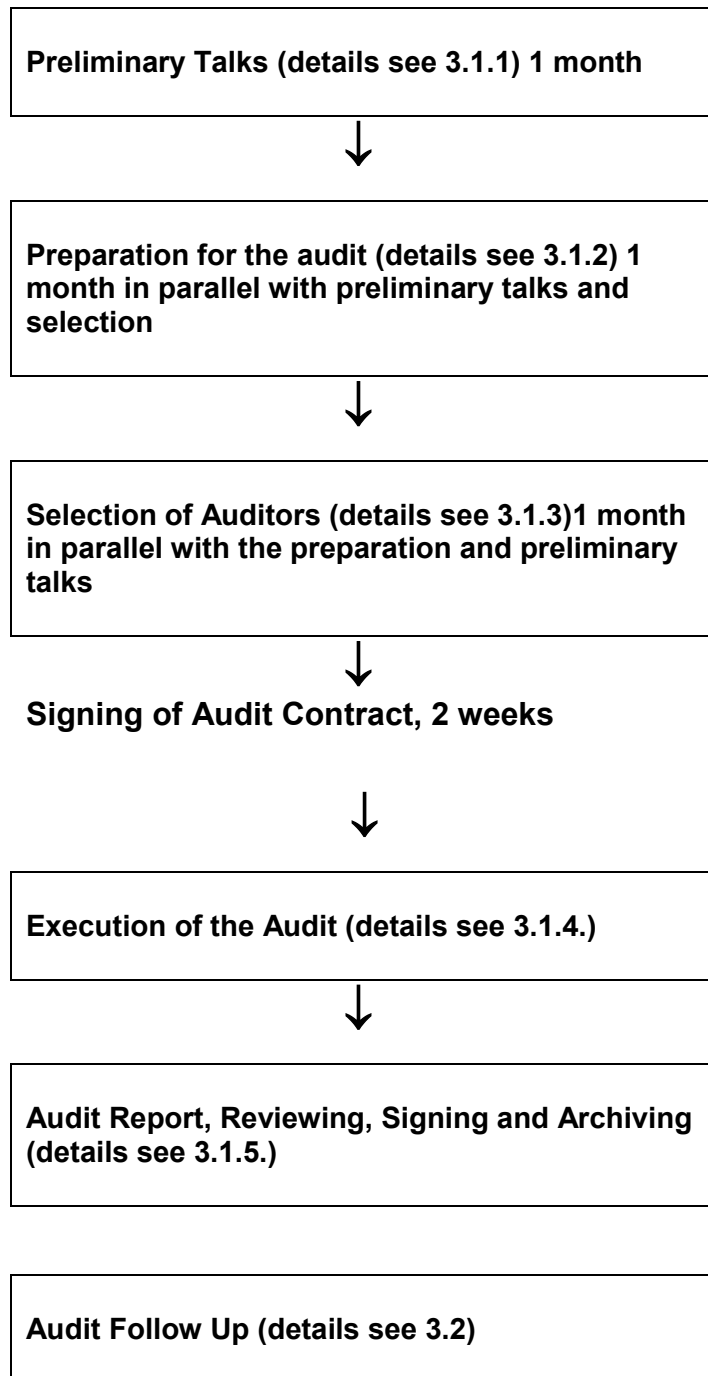
3.3 Contract

Auditors who qualify to become 'APIC Certified Auditors' and who agree to conduct audits in the framework of the APIC Audit Programme have to sign a contract with the API Compliance Institute (see Annex 1). This contract lays down the obligations of the Certified Auditor.

4 The Audit Process

4.1 Steps of the Audit Process

The following section describes the steps that should be followed in the audit process from the initial contact with the API Compliance Institute by the potential customer until the distribution of the audit report.



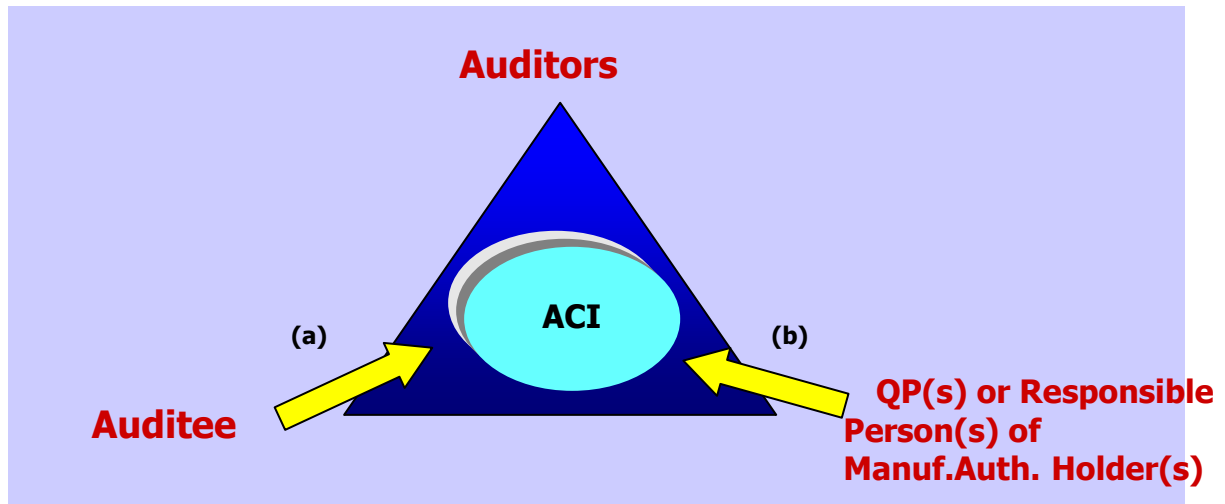
4.1.1 Preliminary Talks

A Third Party Audit should be initiated by one or more QP(s)/ or responsible person of Manufacturing Authorisation Holder(s) ('called 'customer').

Requests to initiate Third Party Audits should be made to the API Compliance Institute in all cases.

Audit requests will follow the Compliance Triangle Principle (see Figure 2).

Figure 2: Compliance Triangle Principle of the APIC Third Party Audit Programme, Preliminary Talks



(a) Request by the Auditee: self assessment of GMP status

(b) Request by the QP(s) or Responsible Person(s) of the Manufacturing Authorisation Holder(s): Third Party Audit of API Starting Material used in Medicinal Products

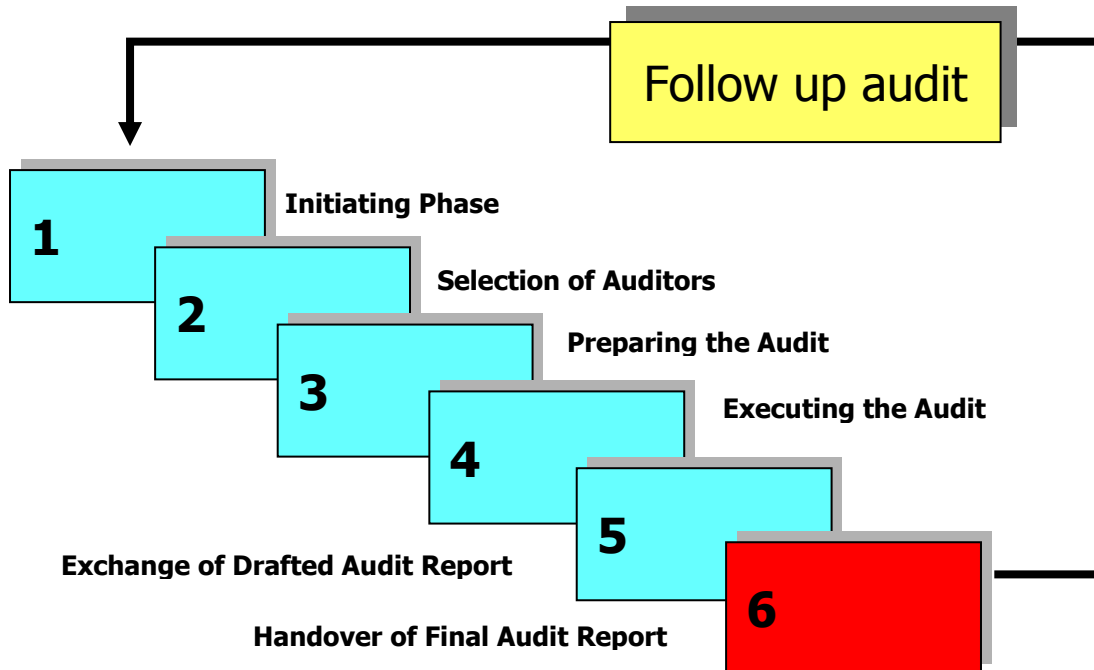
Before formal placement of an order by the customer, the API Compliance Institute will have preliminary talks on the following topics, among others:

- Provide details of the objectives and structure of the APIC Audit Programme so that the customer can verify that the audit process is suitable with respect to Chapter 7 of EU GMP Guide relating to Contract Services.
- Scope of the audit
- Steps of the audit process
- Expected time inputs and expected costs
- Sample of an audit report, if desired
- Timetable, if desired
- Discuss potential involvement of other customers with the API Manufacturer and initial customer requesting audit to encourage Shared Third Party Audit Option.
- Standardised letters (Annex 4) to encourage The Shared Third Party Audit Options will be sent by the ACI to the Manufacturing Authorisation Holder and

Auditee to explain the Shared Third Party Audit Option and if they are in agreement, the relevant Standardised Letters may then be sent to other Manufacturing Authorisation Holders who may be interested in participating in the Shared Third Party Audit.

The following standardised approach will be followed.

Figure 3: Standardised Audit Process



If the customer is interested in ordering an audit, the API Compliance Institute will send the necessary documents, including the Audit Agreement (see Annex 2) to the customer. The customer can define any specific points that should be covered in the audit for example corrective actions from previous audits in the amendment to the Agreement.

The Audit Agreement has to be signed by all parties involved, the) ('customer'), the Auditee, the auditors and the API Compliance Institute. When more than one QP or Responsible Person(s) of the Manuf.Auth.Holder are requesting the audit, for reasons of confidentiality, contracts with each QP can be documented separately.

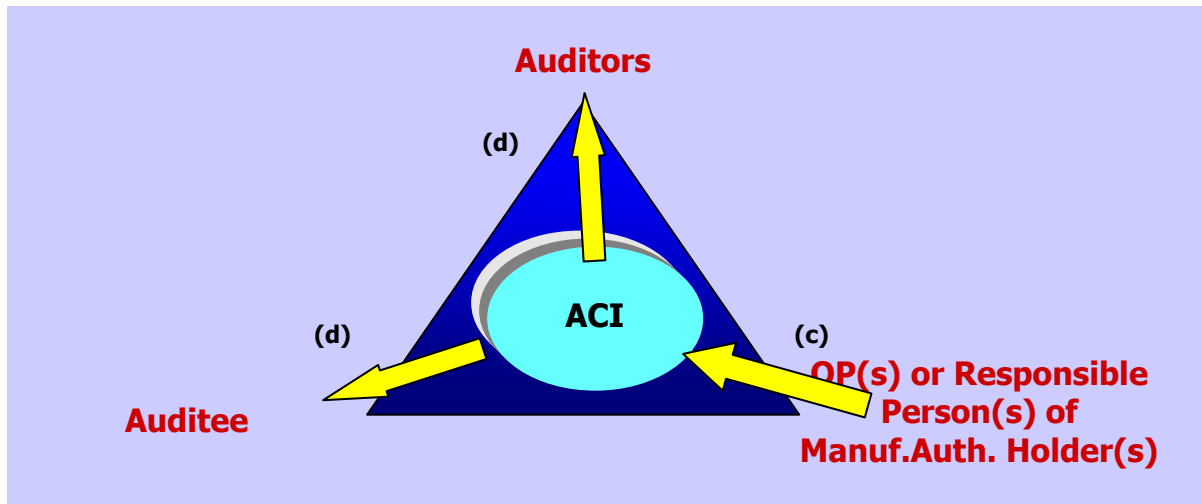
In case of a 'self-assessment audit, the Audit Agreement has only to be signed by the customer as Auditee, the auditors and the API Compliance Institute.

The services listed in the following sections on the individual steps of the audit take place after the Audit Agreement has been signed by all parties and returned to the API Compliance Institute.

A Secrecy Agreement that is designed to protect the confidential information of the Auditee will be prepared and signed. A proposed Secrecy Agreement is available in [Annex 3](#).

4.1.2 Preparation for the Audit

Figure 4: Step (1): Initiating Phase



(c) QP(s) contact(s) ACI

(d) ACI contacts the Auditee and sends the pre-audit questionnaire and contacts two APIC certified auditors

For gaining initial information about the Auditee and to effectively plan the audit a pre-audit questionnaire (for further details see Appendix B of APIC Auditing Guide) will be sent by the API Compliance Institute to the Auditee in advance.

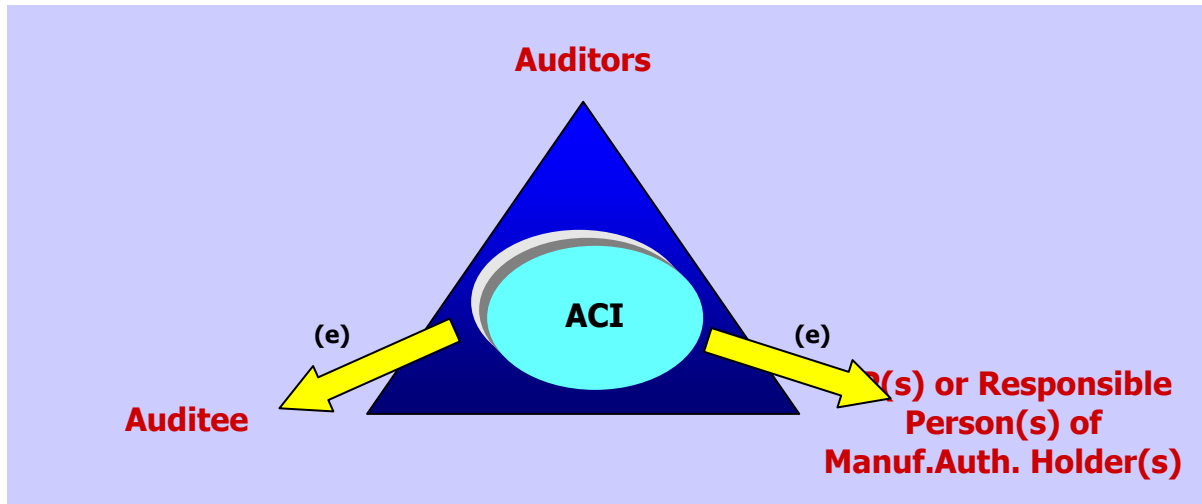
After return of the completed questionnaire, two auditors will be selected by the API Compliance Institute according to section 3.1.3 based on the information given in the questionnaire.

The questionnaire will also be handed on to the selected auditors for their preparation. In the case the audit is initiated by one or more ('customer'), the filled-in questionnaire will be handed on to each 'customer'. If, after evaluation of the questionnaire, the auditors will have any doubt of a successful audit, the Auditee and the customer(s) will be contacted by the API Compliance Institute to discuss on how to proceed.

The Auditee will appoint a contact person (audit representative) responsible for the handling of the audit.

4.1.3 Selection of Auditors

Figure 5: Step (2): Selection of Auditors



- (e) ACI informs the Auditee and the QP(s) about the names of the chosen APIC certified auditors. Both the Auditee and/or the QP(s) can refuse one or both auditors (e.g. due to competition reasons)

In general, the API Compliance Institute will select two Certified Auditors from the APIC register. A lead auditor will be nominated. The Auditee and the customer(s) will be notified of the names of the auditors.

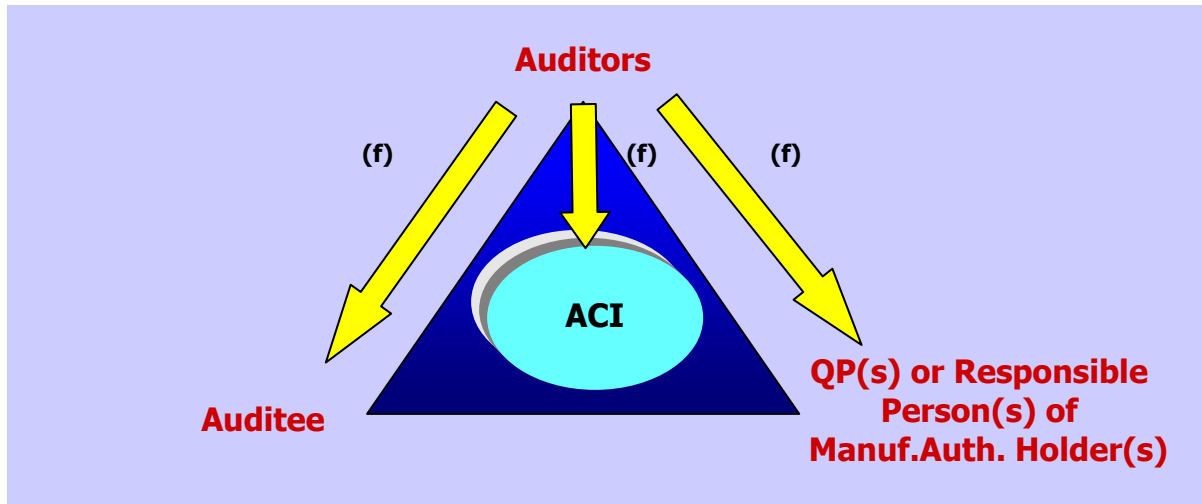
The Auditee and the customer(s) are entitled to reject the proposed auditors. Nevertheless they will be asked to explain the reasons for rejecting an auditor. In these cases new auditors will be selected by the API Compliance Institute. On request the Auditee and the customer will be informed on the types of audits the auditor(s) has/ve conducted during the past two years.

After agreement on the choice of auditors, a Secrecy Agreement (Appendix 3) will be signed by the API Compliance Institute, the customer(s), the Auditee and the Auditors. Company Secrecy Agreements may also be used.

The auditors will sign a statement in the Secrecy Agreement to confirm that they did not work for the Auditee or customer (for example as a consultant or employee) for at least 5 years prior to the audit and there is no financial interest or commercial conflict with customer or Auditee.

4.1.4 Execution of the Audit

Figure 6: Steps (3) and (4): Preparing and executing the audit



- (f) Lead Auditor interacts directly with the Auditee in order to plan the audit in detail, keeping the QP(s) and ACI informed.

As a guideline, the audit may be performed by two auditors for two days. The customer has the responsibility to define the duration of the Audit and number of auditors if more or less time/auditors are required to meet their requirements dependent on the scope of the audit.

Before the audit, the customer(s) and the Auditee will receive an audit plan from the auditors, detailing the major topics of the audit and a tentative schedule. Agreement must be reached on the proposed audit plan from all parties involved (customer(s), Auditee and auditors) before the audit can take place.

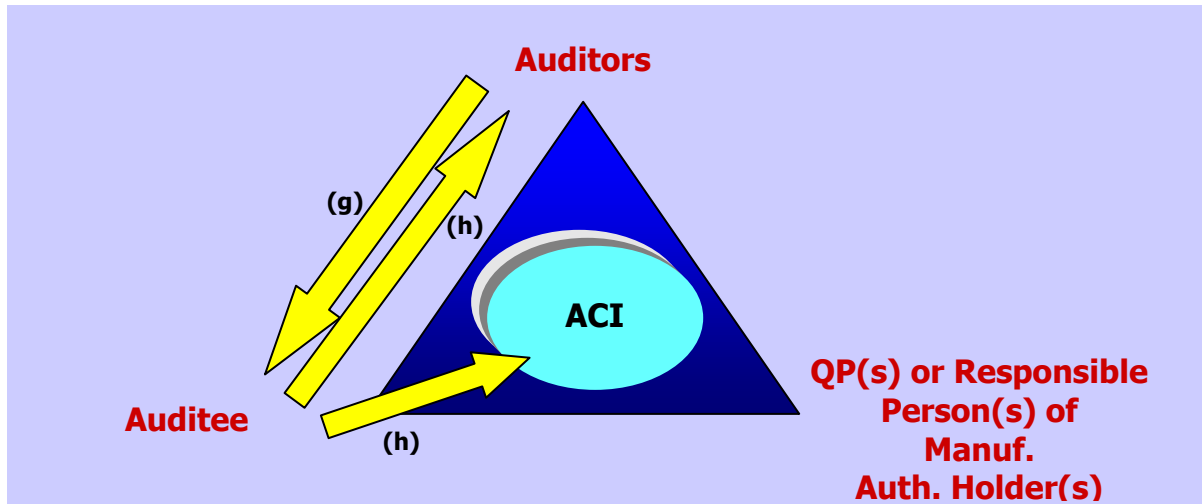
During the audit the GMP compliance of the Auditee will be evaluated by the auditors on the basis of the ICH Q7 guideline (GMP for APIs, part II of the EU GMP Guide) using the APIC Auditing Aide Memoire and APIC How To Do ICH Q7 Guidance document as references.

All observations relating to GMP deficiencies will be explained, clarified and classified (Refer to section 1 for classification rating) during the final wrap up meeting with the Senior Management of the Auditee.

In the case where the API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer requests the Third Party Audit as part of a Self Assessment of GMP status, a 2-day audit performed by 1 auditor may be sufficient.

4.1.5 Audit Report: Reviewing, Signing and Archiving

Figure 7: Step (5): Exchange of draft audit report



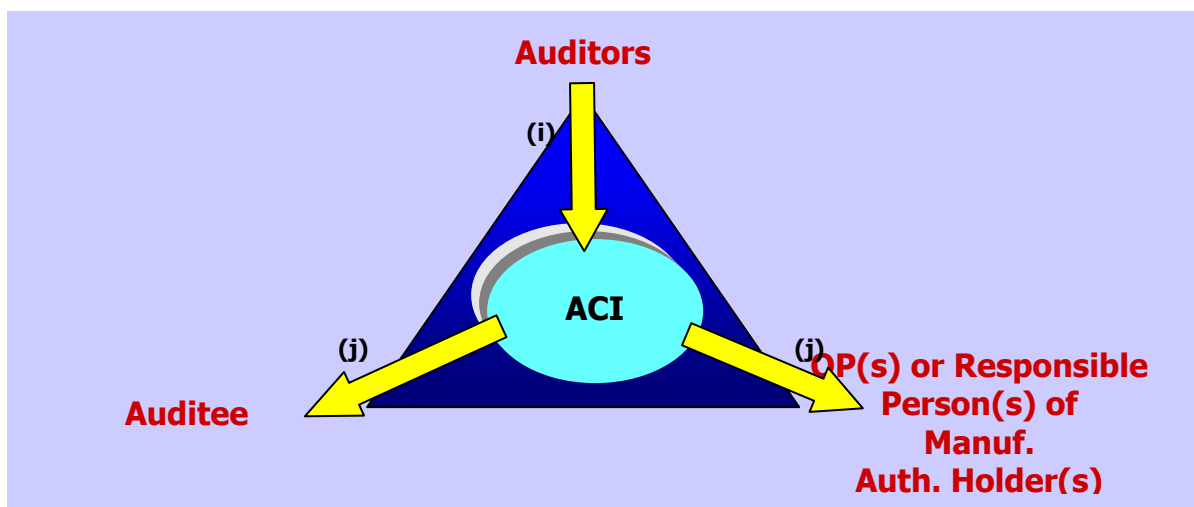
(g) Lead Auditor sends the draft audit report to the Auditee for any missing data, errors in data etc.

(h) After checking the draft audit report for accuracy, the Auditee responds to any observations proposing corrective actions, amends these parts to the final draft of the report and sends it back to the auditors and the ACI.

IMPORTANT: In the drafted report only 'factual' mistakes should be corrected.

At the latest, within a period of 3 working weeks after the audit, the lead auditor sends a drafted audit report to the Auditee to check for accuracy. The audit report will include a management summary, an overview of which ICH topics were evaluated during the Audit, supported by the ICH Q7 checklist and a detailed description and evidence of the deficiencies. The Auditee should check the accuracy and respond to any observations, proposing corrective actions, responsibilities and time frames within one month and amend these parts to the final draft of the audit report that will be sent back to the auditors and the ACI.

Figure 8: Step (6): Handover of the final audit report



- (i) After having reviewed that proposed actions have been defined for any deficiencies the auditors sign the final audit report that is sent to the ACI.
- (j) The ACI sends copies of the signed audit report to the customer(s) and to the Auditee and archives the original signed audit report.

On receipt of the audit report from the Auditee, the auditors will review and confirm that a response with realistic timelines has been received for each observation, sign the audit report and send it to the API Compliance Institute. The ACI will then issue a copy of the final signed audit report to the customer(s) with an authorised copy to the Auditee.

The original signed audit report remains valid for 3 years and will be archived for an additional 7 years by the ACI.

The customer(s) are responsible to review the signed audit report received and decide if any deficiencies have been adequately addressed.

The evaluation of the impact of the audit deficiencies included in the audit report on the GMP status of the API(s) used in the Manufacture of Medicinal Products is the responsibility of the QP(s) or Responsible Person(s) of Manufacturing Authorisation Holder(s) or the Customer in the case of a self-assessment audit.

4.1.6. Resolution of disagreement with GMP deficiencies / performance of auditors.

In the case that the QP or Responsible Person of Manufacturing Authorisation Holder or Auditee is not satisfied with the quality of the audit report / performance of the auditors, they should contact ACI in writing explaining their concerns. ACI will review their concerns with the auditors and QP or Responsible Person of the Manufacturing Authorisation Holder and try to satisfy the concerns.

In the case that there continues to be a serious disagreement on any of the deficiencies made in the audit report or in the performance of the auditors, the ACI

may also request independent review from the APIC Audit Programme Representative / APIC Exec Member on the GMP Compliance issues raised. In this case, the ACI should ensure there is no Conflict of Interest with the APIC Nominee and the Auditee and the terms of the Confidentiality Agreement should be extended to include this review.

The ACI will report in writing to the QP or Responsible Person of Manufacturing Authorisation Holder and the Auditee to give feedback on the formal review of their disagreements and request agreement to close the audit report.

In the case that resolution of disagreements is not possible and the disagreements are related to poor audit performance, the Audit Agreement will be revoked. Written statements of the auditors, the auditee and the customer will be included into the audit report.

IMPORTANT: The copyright of the audit report is jointly held by the customer(s), Auditee and API Compliance Institute. If any of these parties wishes to pass on the audit report to a subsequent Third Party, a request should be made to the API Compliance Institute who is responsible to ensure that all parties agree to sharing of the Third Party Audit Report.

If any party disagrees, then further sharing of the Third Party Audit reports will not be allowed by the API Compliance Institute.

If all parties agree, the API Compliance Institute will discuss the use of the Third Party Audit Report with the subsequent customer to ensure the scope of the audit meets their requirements before the audit report is shared.

With the agreement of the Auditee, a list of Third Party Audits completed within the last 3 years may be published on the ACI Website.

IMPORTANT NOTE. It is an essential condition of the Audit Agreement that All Parties agree in advance of the audit that the audit reports may be shown to European Union Member State Inspectors during an audit of the Manufacturing Authorisation Holder(s) as evidence for the qualification of the API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer. This requirement is included as a standard clause in the Audit Agreement.

4.2 Audit Follow-up

Following completion and issue of the Third Party Audit Report, the Auditee should issue periodic updates on progress with proposed actions to the customer(s) based on the timelines defined in the audit report.

The Manuf.Auth.Holder(s) have the responsibility to check that the proposed actions of the Auditee in response to the audit observations have been implemented in a timely and effective manner.

The Manuf.Auth.Holder(s) will also decide on the need and timing for a follow up audit including auditing of the effectiveness of the corrective actions defined in original audit report.

4.3 Audit Feedback

Within one month of completion of the audit report, the ACI will request feedback on the effectiveness of the audit process and performance of the auditors from the Auditee using the standard form (Appendix 5). Feedback on displayed knowledge

and understanding of the GMP requirements for APIs, audit performance, general communication and inter-personal skills of the auditors will be requested.

This feedback will be used by ACI to improve the effectiveness of the audit programme and to assess the performance of the auditors on an ongoing basis and will be reviewed during the evaluation of auditor performance at the time of their Re-Certification as APIC Auditors.

5 Costs Considerations

The costs of an audit will be calculated

- on a fee per diem rate and
- reimbursement of travelling of the Auditors.

An audit of an API site normally lasts 2 days and will be conducted by 2 auditors. In addition, 1 day of preparation and 1 day of write-up / follow-up are calculated.

Standard Audit cost is 8,400 €.

In case of intercontinental traveling (outside Europe and the African countries adjacent to the Mediterranean) an extra charge of 1.200 € will be invoiced.

Costs for a Shared Audit depend on number of QP(s) / customers involved. The costs of the audit will be divided through the number of QP(s)/ customers involved with a handling fee per customer added.

The travel and accommodation costs of the auditors will also be allocated pro rata. If the length of the Audit or the number of Audits are reduced, then the costs of the Audit will be reduced accordingly.

Example

Fee for a standard Third Party Audit: 8.400 €

Shared Third Party Audit initiated by 5 sharing partners

Total costs: $8.400 \text{ €} : 5 = 1.680 \text{ €} + 200 \text{ €}$ (handling fee): 1.880 €

Shared Third Party Audit initiated by 10 sharing partners

Total costs: $8.400 \text{ €} : 10 = 840 \text{ €} + 200 \text{ €}$ (handling fee): 1.040 €

Additional costs in form of expenses (e.g. hotel, flight tickets) will also be divided through the number of sharing partners and will be invoiced separately

In all cases the statutory value added tax will be added.

In the case that a completed Third Party Audit Report is requested by subsequent customers, re-imbusement costs will be given to the original customer(s) for the Third Party Audit until all costs of the initial audit have been reimbursed.

Example:

Audit report costs to a subsequent customer: 1.500 €

The original sharing partners will be reimbursed **750 €** (50%) proportionally.

Reimbursement for 5 original sharing partners

750 € : 5 = **150 €** for each original sharing partner

Reimbursement for 10 original sharing partners

750 € : 10 = **75 €** for each original sharing partner

In all cases the statutory value added tax will be added.

6 Relationship between APIC and the API Compliance Institute

There is an Agreement between APIC and the API Compliance Institute that defines the responsibilities of each party.

Table 1 lists the major obligations of the API Compliance Institute and APIC.

Table 1: Major obligations of the API Compliance Institute and APIC

API Compliance Institute	APIC
<ul style="list-style-type: none"> • Design of the Auditor qualification seminars (see 2.2) • Organisation and execution of the qualification seminars and examinations for Certified Auditors • Maintenance of Current list of APIC Certified Auditors • Coordination of the APIC Third Party audits • Steps of the audit process: <ul style="list-style-type: none"> - Preliminary Talks (see 3.1.1) - Preparation for the audit (see 3.1.2) - Selection of Auditors (see 3.1.3) • Administration and archiving of the audit reports for 7 years • Compilation of an annual report for APIC 	<ul style="list-style-type: none"> • Providing speakers for the Auditor training courses; • Involvement of APIC Executive and Quality Working Group members in Auditor training courses • APIC lead representative for audit programme to be involved in Auditor qualification courses and to evaluate suitability of candidates for APIC Certified Auditors • APIC lead representative for Audit programme or APIC EXEC Member to give independent review of any serious objections from the Auditee / customer to GMP Deficiencies and classifications - at the request of API Compliance Institute

APIC will review, on a regular basis, together with the API Compliance Institute the function of the "APIC Audit Programme" process and will agree any areas of improvements.

APIC will not intervene in the responsibilities of the API Compliance Institute related to this programme and will not request specific information related to audited companies such as audit reports.