



# The APIC Audit Programme

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# The APIC Audit Programme

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## 1 General

According to the revised 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 EMEA Website GMP Question and Answers on audits of active substances manufacturers (<http://www.emea.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 (MA Holder) of their Active Pharmaceutical Ingredient (API) Manufacturers / Suppliers should be an integral part of the Supplier Qualification Procedure of the MA 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 MA Holder.

If a Third Party is involved then the MA 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.

In view of the legal background and the GMP expectation of supplier evaluation by the authorities, the Qualified Person of the MA Holder is responsible to assure that the APIs used in 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 MA Holder for each API Manufacturer.
- A **Third Party Audit** of the API Manufacturer performed on behalf of the QP of the MA Holder. The QP (Contract Giver) confirms that the Third Party Audit Process provides an effective assessment of the GMP status of the API manufacturer and 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 of each Manufacturing Authorisation Holder ensures that the scope of the audit is applicable to each Medicinal Product that uses the API as Starting Material.

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

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 Qualified Person (QP) of the Holder of the Manufacturing Authorisation for the purposes of complying with the EC Directives and Guidances described above.

In the case that several QPs of MA 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 by a QP, both the API Manufacturer and the QP may contact other QP's of MA Holders to let them know that a Third Party Audit Request is ongoing and if they wish to share in this audit, they should contact the API Compliance Institute.

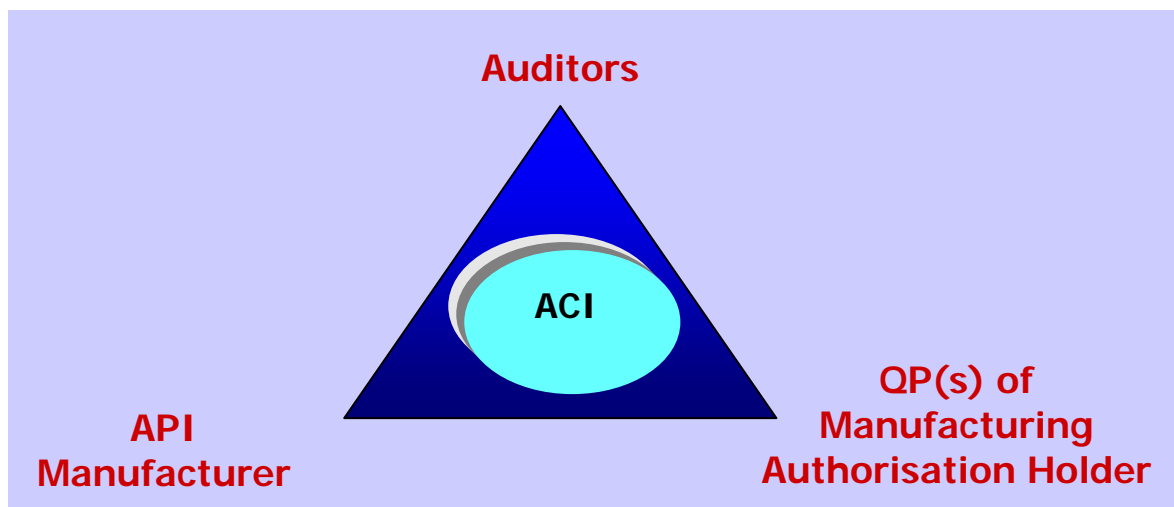
In the case that a Third Party Audit has recently been performed and the API Manufacturer is contacted by a QP of another MA Holder who is interested in assessing whether this Third Party Audit Report satisfies their requirements, the QP should be asked to contact the API Compliance Institute.

In the case that the API manufacturer 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** of the GMP status of the API Manufacturer, so it cannot replace the MA Holder initiated audits.

**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 QP(s) as 'customer', the API manufacturer as 'auditee' and / or customer, 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**



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 process.

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 Distributor is performed and that full documentation is available to describe the audit.

The audit report will include detailed 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):

**Critical**

The condition will seriously affect the quality of products or regulatory compliance. The condition violates essential GMP-rules and basic quality assurance practices. Immediate action should be taken.

**Major**

The condition may affect the quality of the product or regulatory compliance. The condition violates GMP-rules and quality assurance practices. Action is required.

**Minor**

The condition may not affect the quality of the product/regulatory compliance. The condition violates current GMP-rules. Action is recommended.

**Recommendation**

Recommendation for quality, safety or efficiency improvement. No GMP violation.

In the case of critical observations being found, the Qualified Person of the MA Holder and / or the API Manufacturer will decide on any further actions necessary, for example Product Recall.

## **2 The Auditors**

### **2.1 'Qualification' versus 'Certification'**

#### **2.1.1 Educational Background and Experience**

Because of the nature of API manufacture, the Auditors generally 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.

#### **2.1.2 Qualification as an Auditor and 'Certification' as an 'APIC Certified Auditor'**

##### **2.1.2.1 Auditor Training Courses for 'Qualification'**

A Qualification training course for Auditors is offered as part of the APIC Audit Programme.

Attendance at a five-day qualification seminar (three days related to GMPs in API manufacture and two days for training in effective auditing techniques) is a prerequisite for qualifying as an 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.

##### **2.1.2.2 Certification of Auditors**

In order to become an APIC Certified Auditor, the 'Qualified' Auditor should undergo an examination. This examination exists 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 Q7A. This written exam is created by APIC in co-operation with the API Compliance Institute. After the seminar, 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 qualification course and a trainer with academic education in psychology assess the auditing skills of the participants during the Qualification Training Course.

The APIC representative judges the participant's aptitude for conducting 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 the examination performance.

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 qualification (see point 2.1.1) 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 another three years provided he/she has attended a recognised training course / conference on current GMP Topics and has satisfactorily performed audits.

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.

## **2.2 Contract**

Auditors who qualify to become 'APIC Certified Auditors' and 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.

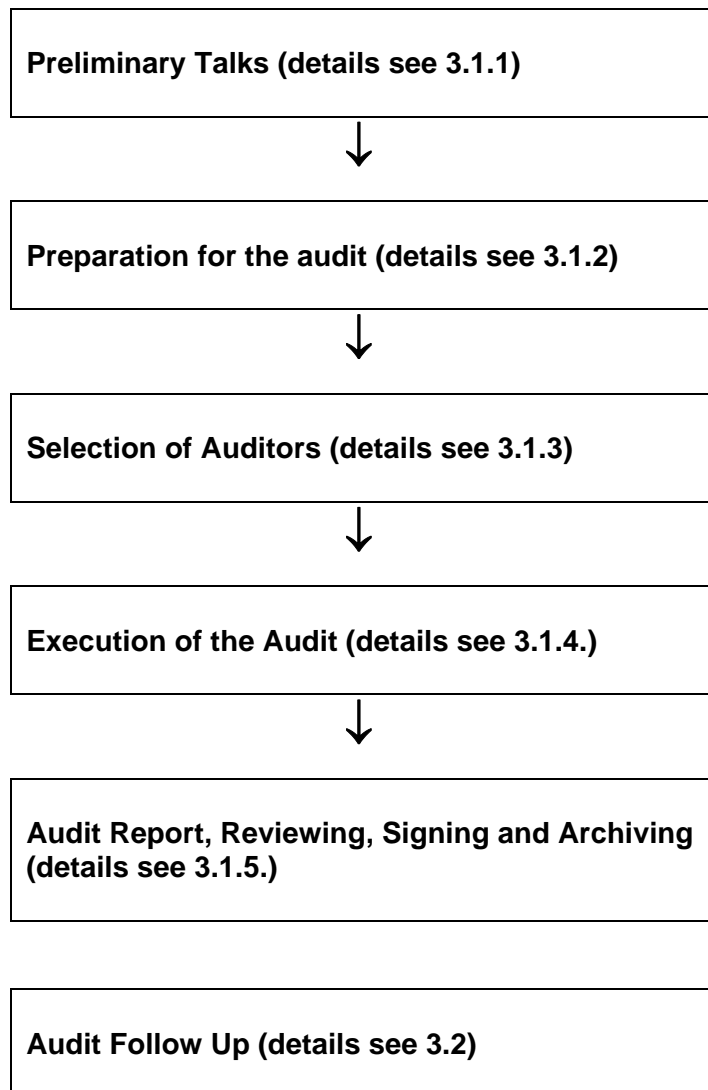
### **3 The Audit Process**

#### **3.1 Steps of the Audit Process**

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

The customer will be the Qualified Person(s) of the MA Holder when the Third Party Audit is being performed as part of the MA Holder's responsibility to assess the GMP Compliance of the API Manufacturer.

The customer will be the API Manufacturer when the Third Party Audit is being performed for the purposes of a Self Assessment of GMP Status.



##### **3.1.1 Preliminary Talks**

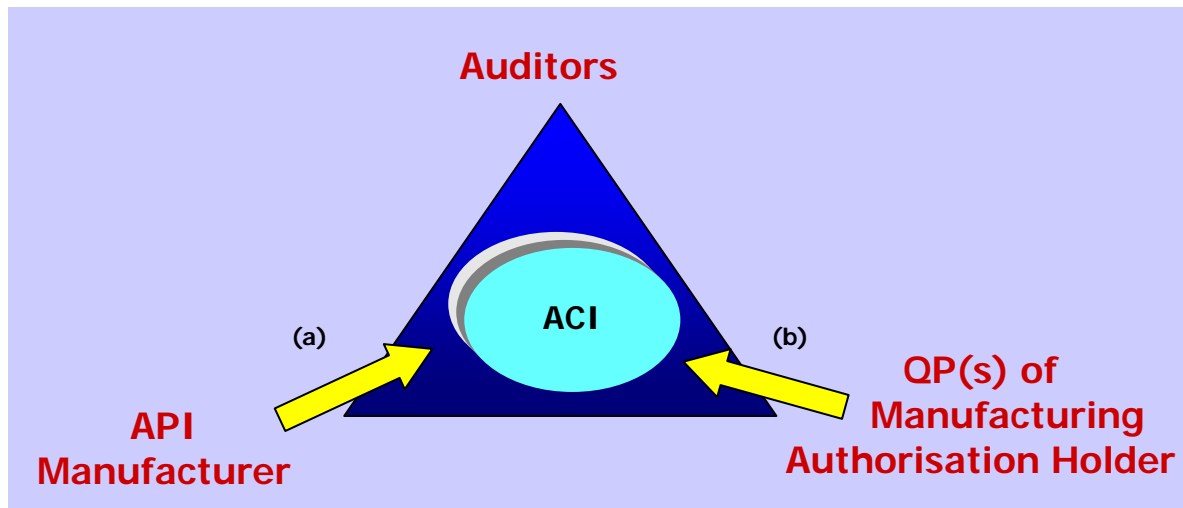
A Third Party Audit of an API manufacturer can either be initiated by one or more QP(s) of the Manufacturing Authorization Holder(s) ('called 'customer') or by the API manufacturer itself (called 'auditee').

If the API manufacturer initiates the audit, the API manufacturer becomes 'customer' and 'auditee' at the same time and the purpose of the audit is a **self assessment** of the GMP status of the API Manufacturer.

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 API manufacturer: self assessment of GMP status**

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

ACI = API Compliance Institute

QP = Qualified Person

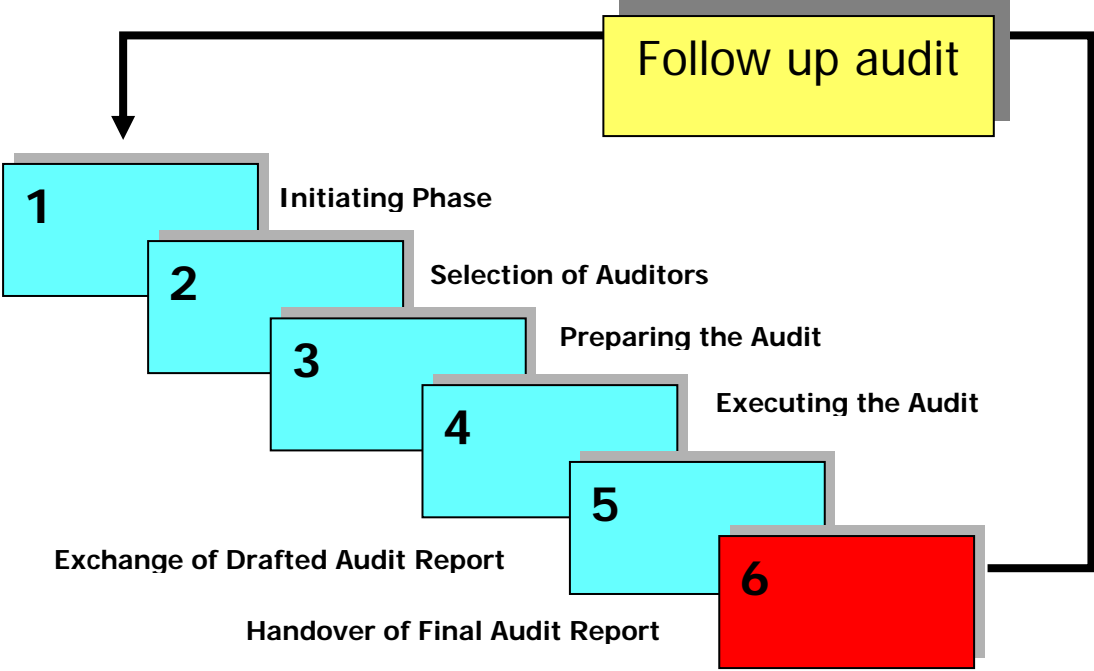
MA Holder = Manufacturing Authorisation Holder

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 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 QPs with API Manufacturer and initial QP requesting 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 QP(s) ('customer'), the API manufacturer ('auditee'), the auditors and the API Compliance Institute. When more than one QP/MA Holder are requesting the audit, for reasons of confidentiality, contracts with each QP can be documented separately.

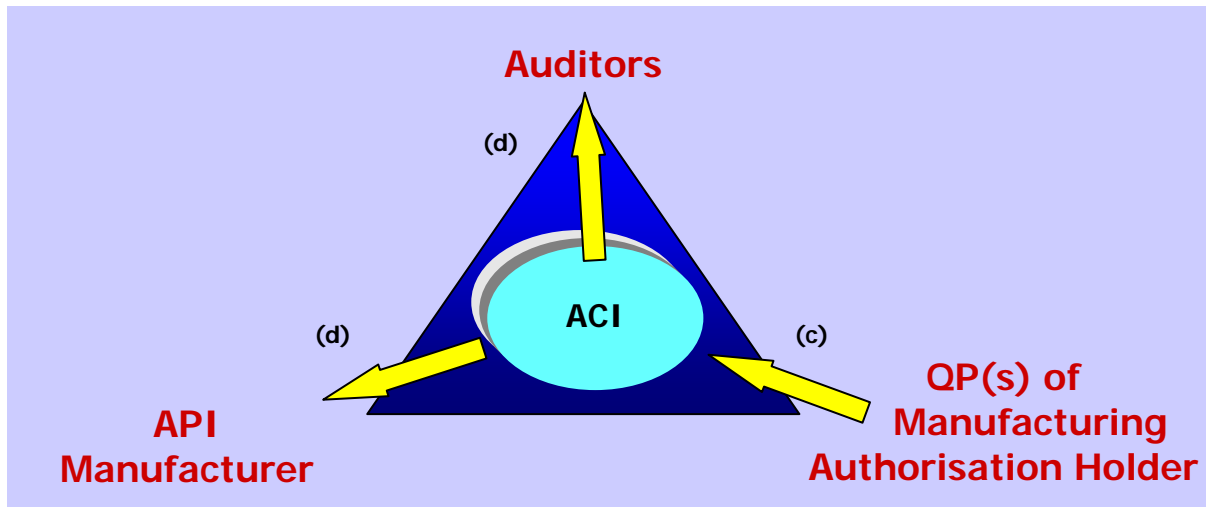
In case of a 'self-inspection' (API manufacturer, who is 'customer' and 'auditee' at the same time), the Audit Agreement has only to be signed by the auditee, the auditor(s) and the API Compliance Institute.

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. Company Secrecy Agreements may also be used.

### 3.1.2 Preparation for the Audit

Figure 4: Step (1): Initiating Phase



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

(d) ACI contacts API manufacturer (auditee), sends 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.

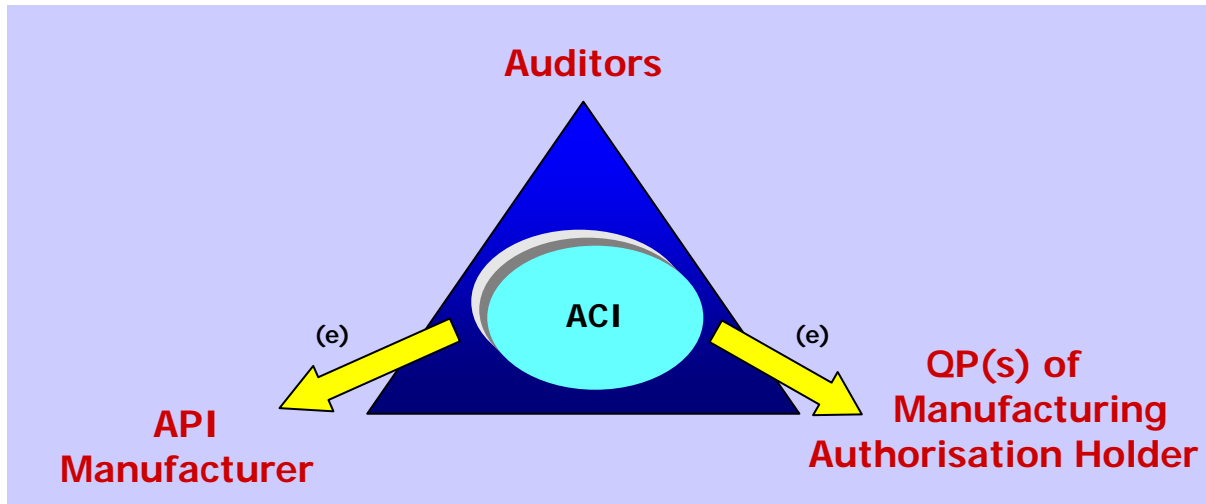
After return of the completed questionnaire, two auditors will be selected by the API Compliance Institute according to section 3.1.3 based on the information given in the questionnaire.

The questionnaire will also be handed on to the selected auditors for their preparation and in case the audit is initiated by one or more QP(s) ('customer'), the filled-in questionnaire will additionally 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.

### 3.1.3 Selection of Auditors

Figure 5: Step (2): Selection of Auditors



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

ACI = API Compliance Institute  
QP = Qualified Person

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.

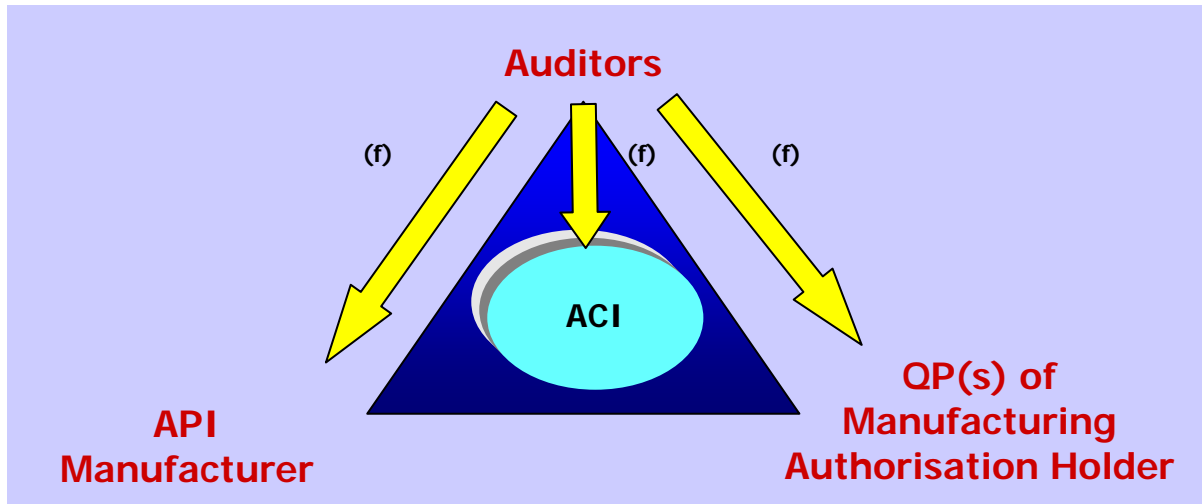
The auditee and the customer(s) are entitled to reject the proposed auditors. Nevertheless they will be asked to explain the reasons for rejecting an auditor. In these cases new auditors will be selected by the API Compliance Institute. On request the auditee and the customer will be informed on the 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.

### 3.1.4 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 rule, the audit will be performed by two auditors for two days. Exceptions (more or less auditors, longer duration) are subject to discussions between the customer(s), the auditee, the auditors and the API Compliance Institute.

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.

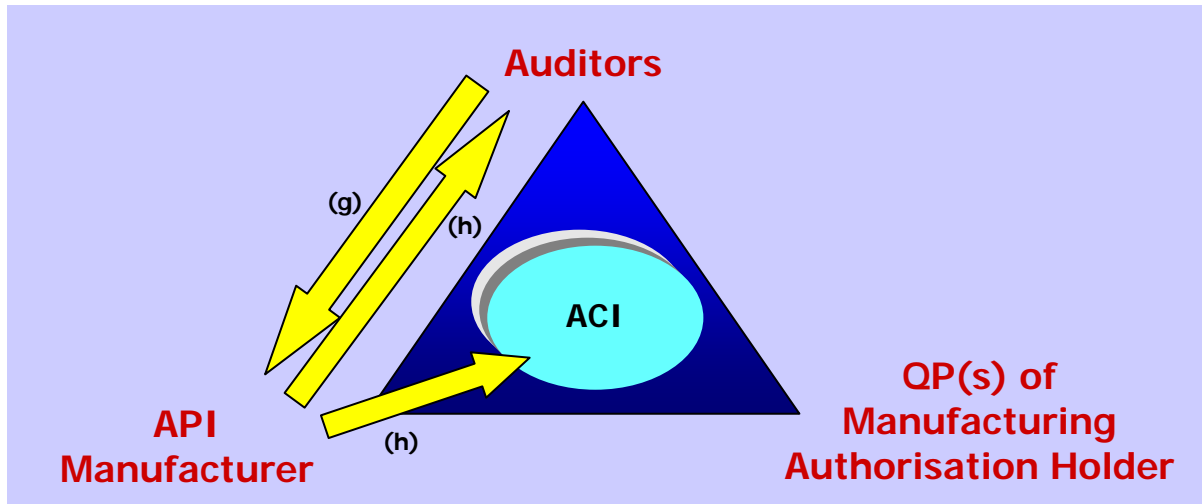
During the audit the GMP compliance of the auditee will be evaluated by the auditors on the basis of the ICH Q7a guideline (GMP for APIs, part II of the EU GMP Guide) using the APIC Auditing Aide Memoire as a reference.

All observations relating to GMP deficiencies will be explained, clarified and classified during the final wrap up meeting with the Senior Management of the Auditee.

In the case where the API Manufacturer 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.

### 3.1.5 Audit Report: Reviewing, Signing and Archiving

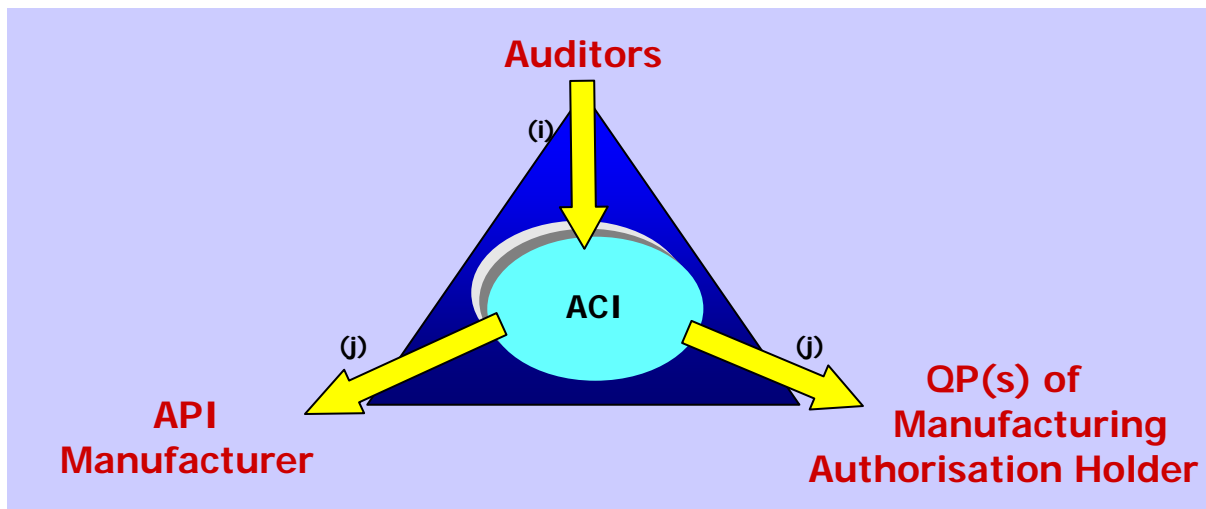
Figure 7: Step (5): Exchange of draft audit report



- (g) Lead Auditor sends the draft audit report to the API Manufacturer (auditee) for any missing data, errata 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 as well as a detailed list of observations and recommendations. 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 observations 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 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 with the ACI for the purpose of archiving for a period of 7 years.

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

The impact of the audit findings 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) of the Manufacturing Authorisation Holder(s) or the API Manufacturer in the case of a self-assessment audit.

**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 are responsible to ensure that all parties agree to sharing of the Third Party Audit Report.

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.

The audit reports may be shown to European Member State Inspectors during an audit of the Manufacturing Authorisation Holder(s) as evidence for the qualification of the API Manufacturer / Distributor.

### **3.2 Audit Follow-up**

Following completion of the Third Party Audit Process, 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 Qualified Person(s) of the MA Holder(s) have the responsibility to check that the proposed actions of the API Manufacturer in response to the audit observations have been implemented in a timely and effective manner.

The QP(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 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.

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.

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

**5 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

<b>API Compliance Institute</b>	<b>APIC</b>
<ul style="list-style-type: none"> <li>• Design of the Auditor qualification seminars (see 2.1.2.1)</li> <li>• Organisation and execution of the qualification seminars and examinations for certified Auditors</li> <li>• Maintenance of Current list of APIC Certified Auditors</li> <li>• Coordination of the APIC Third Party audits</li> <li>• Steps of the audit process:               <ul style="list-style-type: none"> <li>- Preliminary Talks</li> <li>- Preparation for the audit (see 3.1.2)</li> <li>- Selection of Auditors (see 3.1.3)</li> </ul> </li> <li>• Administration and archiving of the audit reports for 7 years</li> <li>• Compilation of an annual report for APIC</li> </ul>	<ul style="list-style-type: none"> <li>• Providing speakers for the Auditor training courses;</li> <li>• Involvement of APIC Executive and Quality Working Group members in Auditor training courses</li> <li>• APIC lead representative for audit programme to be involved in Auditor qualification courses and to evaluate suitability of candidates for APIC Certified Auditors</li> </ul>

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.

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# The APIC Audit Programme

## *Annex 1*

### Contract between Auditor and the API Compliance Institute

## AGREEMENT

between

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(hereinafter referred to as the "Auditor")

and

API Compliance Institute  
Rischerstr. 8  
69123 Heidelberg

(hereinafter referred to as the "ACI")

## **§ 1 Nature of the Agreement**

The parties agree on a co-operation defined within the framework of this agreement for conducting audits by the Auditor on behalf of the ACI. This agreement defines the tasks and obligations of the Auditor. It does not define any obligation for the ACI to assign the Auditor on a regular basis.

Both parties intend to continue this co-operation for further audits unless one of the options described in §10 apply.

## **§ 2 Obligation of the Auditor**

The Auditor must have a valid certificate for auditing, issued by CEFIC/APIC.

The Auditor will act independently of the ACI during the audits; he is not bound to any instructions and takes all assessments based on his/her own judgment.

The Auditor cannot be recruited for an audit if his/her employer is in competition to the Auditee. By signing this Contract, the Auditor undertakes to confirm that he/she has not performed consulting activities for the customer and/or Auditee for at least five years before agreeing to take part in an APIC Third Party Audit.

## **§ 3 The Audit**

The ACI will assign audits to the Auditor based on the demand and availability of the Auditor. The ACI will determine if the Auditor acts as lead Auditor or Co-Auditor for a certain audit.

Before assignment the ACI will check the availability of the Auditor.

## **§ 4 Tasks of the Auditor**

The Auditor shall perform audits for the number of days specified by the customer and the Auditee as confirmed by the ACI.

The ACI will send the completed pre-audit questionnaire together with the accompanying documents from the Auditee to the Auditors for the purpose of preparation. It is expected that the Auditors will familiarise themselves with the information provided by the Auditee prior to the audit. The Auditors may require additional information from the Auditee. Therefore, the Auditors may get in direct contact with the audit responsible person of the Auditee. After the completion of the Audit, the Auditors shall return the questionnaire and the accompanying documents to the ACI.

The Auditor will be informed of his / her partner by the ACI in due time.

The Auditor(s) provide(s) an agenda to the Auditee and Customer and seek(s) for agreement before the audit.

Details of the audit, including shifting of days, may be arranged by the Auditor(s) and the Auditee / customer themselves together with a notification to the ACI.

It is the responsibility of the Auditor(s) to provide an Audit Report no longer than 3 weeks after the audit was conducted. The deficiencies noted during the audit must be classified and reported verbally at the audit closure meeting.

The Auditor(s) are responsible to ensure responses are given by the Auditee to any GMP deficiencies included in the audit report.

## **§ 5 Charging**

The Auditor will be paid EUR 600,-- per day for each day of the audit. In addition he will receive a single payment of EUR 600,-- for preparation of the audit and preparing the Audit Report.

In cases of intercontinental traveling (outside Europe and the African countries adjacent to the Mediterranean) the Auditor will receive an additional payment of one day. The amount of payment will be negotiated on an individual basis.

The charging will be done after the final Audit Report is provided.

In cases the preparation of the Audit Report will be delayed (i.e. more than 3 weeks) the Auditor(s) payment will be reduced by half of his daily charge for each week of delay.

## **§ 6 Reimbursement of Travel Costs**

The customer will administer travel arrangements and the hotel accommodation for the Auditors. This will ensure that the costs are in line with the travel policy of the customer and that costs are minimised. Costs not directly paid by the customer will be reimbursed by ACI. Costs will only be reimbursed on the basis of receipts.

## **§ 7 Confidentiality**

The parties undertake to maintain reciprocally strictest confidentiality about the business matters and trade secrets of all involved parties, the auditors, the customer(s) and the auditee.

Confidentiality in the course of the co-operation remains even beyond termination of the co-operation, unless purpose and object of the agreed co-operation demand otherwise and thereafter only after an appropriate understanding has been reached.

Any departure from this paragraph requires prior written consent of the contractual partners.

The ACI shall not be liable for compensation for this confidentiality obligation.

The Auditors are obliged to sign a secrecy agreement with the customer and/or Auditee for each audit. A proposed secrecy agreement is available in Annex 3 of the APIC Audit Programme.

### **§ 8 Liability for withdrawal and non-performance**

Should any of the parties to this Agreement withdraw from the Agreement or not perform its contractual duties it shall be liable to indemnify the other party for any damage arising from it.

### **§ 9 Issuing of statements**

Neither the Auditor for the ACI nor the ACI for the Auditor are authorised or empowered to represent the respective other party in legal transactions or to issue statements of knowledge and/or consent and/or perform other actions in the name of the respective other party.

In order to avoid misunderstandings, this factor will be emphasized appropriately at all times vis-a-vis third parties.

### **§ 10 Cancellation**

The agreement becomes invalid with immediate effect if the Auditor does not renew his certification by participating regularly (at least every three years) in a recognized GMP Conference/Course and reporting the number of audits performed during this period.

The Auditors may terminate the agreement at any time by notifying the ACI in writing.

The ACI is allowed to cancel the agreement in cases of serious concerns about the Auditors ability of auditing, knowledge about the subject and/or behaviour towards the Auditee or the customer. In case of disagreement by the Auditor, CEFIC/APIC will take a definite decision.

## **§ 11 Place of Jurisdiction**

The venue for any legal action shall be Heidelberg, Germany. This Agreement shall be governed by German law.

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Date, Location, Signature of the Auditor

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Date, Location, Signature of ACI



# The APIC Audit Programme

## *Annex 2*

### Agreement on Audit Execution

between

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**(Qualified Person (QP) of the Manufacturing Authorisation Holder, hereinafter referred to as "Customer".)**

In case of more than one QP ('shared audit') all 'customers' have to be listed here or separate agreements are signed for reasons of confidentiality.

and

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**(API manufacturer to be audited, hereinafter referred to as "Auditee")**

When the API manufacturer initiated an audit himself for the purpose of 'self-inspection', the API manufacturer becomes 'customer' and 'auditee' at the same time.

and

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**Lead Auditor**

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**Co-Auditor**

**and**

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**API Compliance Institute  
Rischerstraße 8  
D- 69123 Heidelberg  
(hereinafter referred to as "ACI" )**

## **§ 1. Subject of the Agreement**

A two-day GMP audit will be conducted on behalf of the Customer by two APIC Certified Auditors in order to verify the degree of compliance of the auditee with the ICH Q7A Guide "GMP for APIs". The observations of the auditors will be compiled in an audit report, which will be sent to the customer and the auditee no later than 3 weeks after completion of the audit. Any GMP deficiencies found during the audit will be classified by the Auditors and reported in the closing meeting of the audit.

If the customer wishes that specific GMP topics relevant to their Medicinal Products Manufacturer are assessed during the audit, these specific points should be amended at the end of this contract. The amendment is issued to the auditors only and a report on these specific points has to be documented separately by the auditors and reported only to the specific customer.

## **§ 2. Selection of Auditors**

The customer and the auditee reserve the right to refuse an auditor selected by the ACI. An auditor cannot be recruited, if his employer is in competition to the customer and/or the auditee and/or the Auditor has performed consulting activities for the customer and/or the auditee for at least five years before the planned audit.

## **§ 3. Date of the Audit**

The audit date will be arranged between the auditee and the Auditors after signing of the agreement on audit execution and after agreement to the nominated auditors by the auditee and the customer.

## **§ 4. Audit Report**

The audit report prepared by the auditors will give objective evidence of any GMP Deficiencies found during the audit and each deficiency will be classified. The auditee will respond to the deficiencies within one month, the auditors will ensure that a response has been received for each deficiency and will then sign the final report and return to the ACI. The ACI will then send copies of the signed audit report to the customer(s) and auditee. The original audit report will be archived by the API Compliance Institute for 7 years.

## **§ 5. Audit Follow Up**

The customer's Qualified Person(s) is responsible to review the proposed actions included in the audit report by the API manufacturer to ensure that the audit deficiencies have been adequately addressed in relation to the GMP Status of the Active Pharmaceutical Ingredients used in the Manufacture of the relevant Medicinal Products.

The API Manufacturer is responsible to provide to each customer periodic updates of progress with the corrective actions based on the timelines proposed in the audit report. The customer is responsible for follow up to check that corrective actions have been appropriately addressed in a timely manner.

The customer will also decide if a specific follow up audit related to the deficiencies is necessary.

## **§ 6. Costs**

The costs of the audit are € 8.400,-- plus value added tax for a one customer audit.

The costs for a shared audit depend on the number of QP(s) involved. The costs of the audit will be divided through the number of QP(s) involved. A handling fee of €200 will be added per customer.

Example:-

Shared audit with 4 QP(s) (customers):

€8,400 : 4 = € 2,100 + €200 (handling fee) = €2,300 per customer.

Additional costs in form of expenses (e.g. hotel and traveling) will be invoiced separately.

## **§ 7. Mode of payment**

The mode of payment is agreed as follows:

50% on placement of order, 50% on presentation of the audit report, without deductions.

## **§ 8. Confidentiality**

Part of this agreement is the secrecy agreement which will be signed by the customer, the auditee and the auditors (see a proposed agreement in Annex 3). The ACI undertakes not to disclose any specific information related to the customer and/or the auditee especially such as audit reports, to any other party unless all parties agree to sharing of the audit report.

## **§ 9. Liability**

1. The ACI shall be held liable in causes to the customer and/or the auditee during the implementation of the Agreement only to the extent that they are the result of gross negligence. In case that the ACI shall be held liable the extent is limited to the costs mentioned in section 6.
2. The ACI shall not be held liable for claims by the Company regarding insufficient performance by the Auditors.
3. The ACI shall not be held liable for unsuccessful inspections by authorities after having been audited under this agreement.
4. The ACI shall not be held liable in the case of users of the audit report are taking measures leading to any kind of financial impact on the Company.

## **§ 10. Copyright**

Following the Compliance Triangle Principle, the copyright of the audit report will be shared by the API Compliance Institute, the customer(s) and auditee.

Any requests to pass on the audit report to subsequent Third Parties should be made to the API Compliance Institute.

Written agreement will be required from the customer(s) and auditee before the audit report may be issued to a subsequent Third Party.

The ACI will archive the original audit report for a period of 7 years.

Copies of the audit report may be shown on request to European Member State Inspectors during inspection of the Medicinal Product Manufacturers.

### **§ 11. Written form**

All modifications and amendments to this offer are only effective if they are agreed upon by the parties involved in writing.

### **§ 12. Legal venue and applicable law**

Legal venue for any disputes shall be Heidelberg. The laws of the Federal Republic of Germany are applicable.

### **§ 13 Salvatory clause**

Should any of the above provisions in this Agreement be invalid this shall not impair the validity of this Agreement. It is to be substituted by the provisions coming closest to the intention of both parties which has to be laid down in writing.

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Place, date and signature of the Customer

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Place, date and signature of the Auditee

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Place, date and signature of Lead Auditor

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Place, date and signature of Co-Auditor

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Place, date and signature of ACI

## **Amendment to Audit Agreement**

The customer should describe in the section below any GMP Topics specific to their use of the Active Pharmaceutical Ingredients that should be reviewed by the Auditors during the audit. The Auditors will provide a separate report on these points only to the relevant customer.

Specific GMP Topics to be covered:

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Place, date and signature of the Customer



# The APIC Audit Programme

## *Annex 3*

### **Secrecy Agreement for the APIC Audit Programme**

between

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(hereinafter referred to as the 'Customer')

**and**

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(hereinafter referred to as the 'Auditee')

**and**

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(hereinafter referred to as the 'Lead Auditor')

**and**

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.....  
(hereinafter referred to as the 'Co-Auditor')

**and**

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.....  
.....

**API Compliance Institute  
Rischerstr. 8  
69123 Heidelberg**

**(hereinafter referred to as "ACI")**

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**§1**

The purpose of disclosure of the information is to enable the auditors to conduct their audit in the facilities of the auditee with a view into the quality related procedures.

**§2**

The auditors herewith declare their independence and assure the auditee of not being employed or supported by a competing company of the customer(s) and/or of the Auditee for at least the last 5 years.

**§3**

The audit will be conducted in a way that is in accordance with the European Competition Law.

The auditee reserves the right to refuse to disclose requested confidential information by the auditor.

**§4**

The auditors agree not to make use of any confidential information provided during the Audit

The Auditors ensure that all confidential information made available during the audit is treated in the utmost and strictest confidence and assures that none of such confidential information is brought to the attention of Third Parties. Only the findings related to the audit observations shall be shared with the Third Parties and not confidential information.

Remark: In the APIC Audit Programme the following Third Parties are involved: The customer(s) and ACI.

**§5**

The auditors acknowledge that the information may possess a special, unique and extraordinary character and that, therefore, would not be adequately compensated by money. Accordingly the auditors agree that in the event of use of the information in breach of its obligation in addition to legal and equitable rights and remedies, the auditee shall have the right to obtain temporary or permanent injunctions against such prohibited disclosure or use.

**§6**

The auditors personally undertake to respect the terms of this Secrecy Agreement and will not disclose confidential information to any Third Party. The Involved Parties in the Audit Agreement - the auditors, the customer(s), the auditee and ACI - undertake to maintain strictest confidentiality about business matters and trade secrets.

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**§7**

This Secrecy Agreement shall come into force at the date of signing by the Involved Parties. As different parties are involved into the signing process, the latest date of signing is the relevant one.

**§8**

The obligations of the auditors under the terms of this agreement shall remain in effect for fifteen (15) years from the date hereof.

**§9**

As the Third Party Audit is coordinated by the API Compliance Institute, this agreement shall be governed by German Law. The venue for any legal action shall be Heidelberg, Germany.

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Date, Location, Signature of Lead Auditor

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Date, Location, Signature of Co - Auditor

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Date, Location, Signature of Customer

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Date, Location, Signature of Auditee

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\_\_\_\_\_  
Date, Location, Signature of API Compliance Institute

**Confirmation of the Auditors**

We, the undersigning

- Hereby declare that we are fully aware of the contents of the Secrecy Agreement signed in order to protect the confidentiality of the information to which we may have access during the performance of the audit.
- Personally undertake to respect the terms of such an agreement and not to disclose any information received during the audit to any third party.

We hereby accept the assignment to render the services stated in this agreement. We declare that we are independent, as we have not acted for the auditee to be audited within the last five years as an employee, in an advisory function or as consultant. We have neither a financial participation in the customer, the auditee nor are we related to the proprietors or the management.

\_\_\_\_\_  
Date, Location, Signature of Lead Auditor

\_\_\_\_\_  
Date, Location, Signature of Co - Auditor

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