Intercompany Protocol for the execution of shared 3rd Party Suppliers Audits

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ISO 17020 GMP Inspection Body

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DOCUMENT HISTORY

Version 1 (28/JUN/2004)

The first version of this document was created, reviewed and ratified by a group of 16 pharmaceutical manufacturing companies. Due to their interest in conducting audits to suppliers, a framework agreement called Intercompany Protocol was developed to perform audits to suppliers in a collaborative manner as well as to sharing information related to suppliers.

The development and coordination of the document and meetings leading to the Intercompany Protocol issuance were done by the company TDV, S.L.

Version 2 (16/DEC/2005)

On December 9th, 2005, the *Asociación Forum Auditorías (AFA)* was formally registered as a Civil Association of Pharmaceutical Companies to conduct shared supplier audits.

In order to update and adapt the document to the new legal framework, a second version of the Intercompany Protocol was developed.

Version 3.00 (05/MAR/2007)

On March 2007 the document incorporated the requirements published by the EMA (*Questions & Answers on audits of active substances manufacturers*), reviewed the periods of the reports validity and established the new confidentiality criteria between the involved parties during the audits.

Version 3.01 addition (14/NOV/2007)

Auditor Qualification program approved in AFA Assembly in chapter 3.2.

Version 3.02 addition (25/NOV/2008)

Audit follow-up program approved in AFA Assembly in chapter 4.5.

Version 4 (February 27th 2013)

The current version of the document includes the changes introduced because of AFA adaptation to the requirements laid down by the ISO17020 and the implementation of the Risk Management in the audits.

Version 4.01 minor change (May 30th 2013)

Minor change in the description of the Education required to the auditors to avoid misunderstandings due the differences in the degrees nomenclature between different countries and the inclusion of the trade of ISO 17020 accreditation body (ENAC).

CONTENTS

1. INTRODUCTION

1.1 Purpose

This protocol constitutes the *Asociación Forum Auditorías'* rules to perform 3rd Party audits, taking as a reference the regulatory frame established by the EU Directive 2001/83/EC[1] (its amendments 2004/27/EC[2] and 2011/62/EC[3]), the EU Directive 2003/94/EC[4] and the EU Directive 91/412/EC[5].

The aim of these rules is guarantee the accomplishment of the following objectives:

- To provide audit reports that allows the Qualified Person of the interested companies deciding about the validation of the audited supplier and if applicable, to sign the QP Declaration.
- Optimization of the cost of the audits.
- Achieving the two previous objectives maintaining the technical rigour at the highest quality level.

1.2 Background

Asociación Fórum Auditorías (hereafter AFA) is an association of Pharmaceutical companies. It was founded in 2005 with the aim of establishing an organized platform to perform joint audits to suppliers according to an Intercompany Protocol (present document) approved by all affiliated members, ensuring the quality, confidentiality and absence of conflict of interest.

Recently, the regulations related with the outsourcing of critical activities and control of the supply chain of raw materials, have clearly and progressively evolved towards a greater demand, focusing the responsibility in the Qualified Person, which is the person responsible of releasing the related medicinal product to the market.

It is also remarkable that in the frame of 2003/94/EC Directive the GMP guidelines have incorporated the Risk Management concept as a basis of the Quality System of the pharmaceutical companies.

AFA has carefully followed from the beginning the regulation evolution and the pharmaceutical companies' needs. This way to understand the audit services has allowed the AFA approach evolution, methodology and range of services. As

1 *DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use.*

2 *DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.*

3 *DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.*

4 *COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.*

5 *COMMISSION DIRECTIVE 91/412/EC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products*

remarkable initiatives, AFA has leaded the preparation of Supply Chain Control Agreement in a work group constituted by representatives of Pharmaceutical Companies, Health Authorities and Distributor companies.

Finally, the Quality System of AFA has been accredited by ENAC (Spanish official accreditation body) according to the ISO 17020 as GMP Inspection body for the inspections to raw materials for pharmaceutical use.

The current update of the Intercompany Protocol pretends to incorporate all the changes related with the previous exposed.

2. SCOPE OF AFA ACTIVITIES

The collaboration agreement scope among the companies regarding the audits to suppliers increases. The current Protocol establishes the initial basis in order to be able to share the audits performed to suppliers in any of the following scopes:

- *Manufacturing of Active Pharmaceutical Ingredients (API)*
- *Manufacturing of Excipients*
- *Manufacturing of Packaging Materials*
- *Contract Manufacturing of Intermediate or Finished Products*
- *Chemical or Microbiological Analysis Contract Laboratories*
- *Distributors*
- *Carriers*
- *Logistics and Warehouses*
- *Information System Design and Development*

3. RULES

3.1 Confidentiality

Confidentiality constitutes one of the key established agreements.

The mission of AFA's Board of Directors is, among others, preserving the confidentiality of the information provided by the affiliates and obeying the confidentiality agreements with the audited companies.

The following information should be considered as "Confidential":

- Relation sponsor – audited company
- Information provided by the audit sponsors
- Information collected during the audit relative to the audited company and their processes
- Audit Reports

Confidential Disclosure Agreements (CDA) should be established in between the four parties involved in the audits; ***Audited companies***, ***Audit sponsors, Auditors*** and ***AFA***.

The criteria under which the CDAs in between the parties are established are as follows:

- **Confidentiality commitments from audit sponsors**

The use of the information received through the audit reports shall be restricted to the process of suppliers' validation and as supporting evidence in front of the Health Authorities or clients. In case of a corporation and, unless it is limited in the corresponding CDA with the audited company, the report could be used by the subsidiaries companies for the same purpose. In case of requiring handing the reports to third parts, the audit sponsor must previously request the authorization to AFA, who at the same time will request the authorization to the audited company.

- **Confidentiality commitments from auditors**

AFA qualified auditors are committed to not disclose the information received during the preparation and development of the audit:

  - Information received from audit sponsors
  - Information collected during the audit, which shall be entirely delivered to AFA.

- **Confidentiality commitments from AFA**

AFA is committed to not disclose the information received from the audit sponsors on what the raw materials or services, related medicinal products, observations, complaints or related projects refers to. AFA shall establish the necessary mechanisms to comply with this requirement. This information will be solely used for conducting the audit.

AFA protects the confidentiality of the information received from audit sponsors by means of the structure of the audit reports. If necessary, reports are divided in a common part related to general GMP aspects, such as organization, documentation, facilities, laboratories, warehouses, etc.; and an specific part associated to a product or products, for each company, including typically contractual aspects, specifications, process validations, complaints, analytical methods, DMF, etc. The results of the audit will be documented in separated reports for each company where both parts are included:

- **Open part**. Shared by all the audit sponsors.
- **Closed part**. Specific for each audit sponsor.

AFA will act as depositary of the information that allows preparing the audit reports. This information will remain available in a repository under the condition established in section 3.5 of this document.

3.2 AUDITORS

3.2.1 Auditor's Profile

The auditors should have the following profile:

Basic Education:

- Advanced University Degree in Chemistry, Pharmacy, Chemical Engineering or similar.
- Good knowledge of the community regulations that apply to the Research & Development, Manufacturing and Distribution of Pharmaceutical products and their raw materials.
- Knowledge of the procedures needed for the marketing authorisation of Pharmaceutical products.

Experience:

- A minimum of 2 years' experience working in an organization regulated by the GxP principles, holding a responsibility position.
- Experience in the processes of pharmaceutical manufacturing and control, chemical synthesis and the validation of these processes or methods.
- Experience in the design or qualification of facilities for GxP purposes.
- Experience in Quality Control organization and technology.
- Experience in the computer systems commonly used in the pharmaceutical industry and chemical environment and its validation.

Personal skills:

- Ability to maintain the objectivity and consistency approach during the audits.
- Communication skills and ability to create an environment that facilitates communication.
- Analytical mind and tenacity.
- Maturity and open-mind.
- Personal integrity.
- Ability for conveying ideas in a clear and concise manner.

3.2.2 AFA's Auditor Qualification Program

AFA has an internal qualification program that consists of:

- Successful attendance to training in audit techniques and auditor skills development.
- Participation as co-auditor in several audits until the assigned senior auditor considers necessary.
- The Auditor's *Curriculum Vitae* and Qualification process will be approved by the *AFA* Management.

3.3 Conflict of interests

The auditors contracted by AFA shall declare the absence of conflict of interests in the following terms:

- The absence of commercial relationship between the organization performing the audit and the organization being audited.
- The absence of personal conflict by the auditor where he has not been employed by the organization being audited in the recent past (i.e. within the last 3 years) nor has not a financial interest in it.

The Declaration shall be done in a written form and must be signed by the auditor.

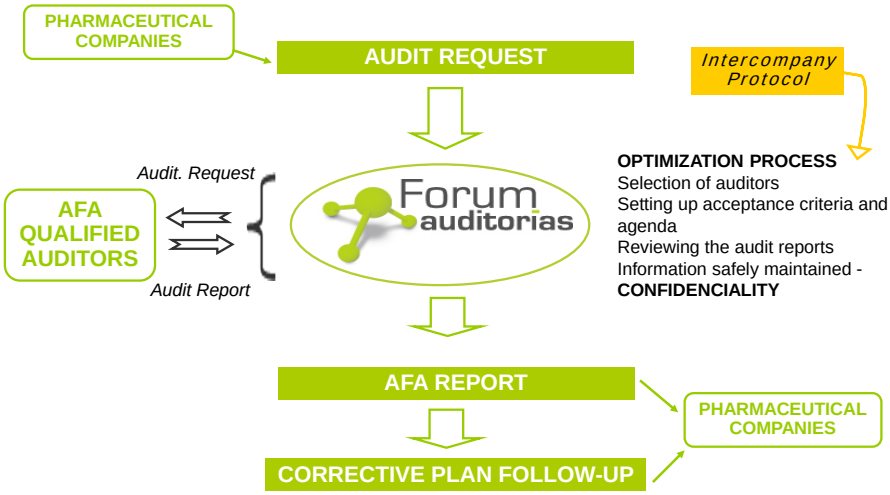
3.4 Audit services contract

Before starting the provision of the audit services it shall be prepared and approved a contract according to the established in EUGMP Part I Chapter 7 "Outsourced Activities". Written agreement/contract between the Contract Giver (audit sponsor) and the Contract Acceptor (AFA) shall clearly establish:

- The duties of each party.
- Technical and organizational issues
- AFA rules and acceptance criteria (refereeing to the content of this document)
- Confidential issues
- Economical offer

3.5 Audits organization

The audits are organized from the request by the pharmaceutical companies that act as an audit sponsors. The audit organization is performed as is showed in the following flow:



Audit sponsors will sign a contract (according to the established in chapter 3.4 of this document). In case of audit packages, a global contract will be issued for the whole audits of interest for each sponsor.

Audit sponsors will send to AFA their specific requirements for the audit.

AFA will contract the auditor team that will perform the audits following the acceptance criteria established in chapter 4.1 of this document and taking into account the specific requirements sent by the sponsors.

The auditor could carry out the audit being accompanied by representative members of the sponsors if interested. However, because of practical reasons, the maximum number of companion is limited to two. Companions will only act as observers without taking part in the auditor's team decisions-making process.

The auditor sends the audit report to AFA for its revision. AFA revision will ensure that all the required information is received is completely comprehensive and the format of the document matches AFA standards.

A separated report is prepared for each audit sponsor.

3.6 Access to the *AFA* Repository

New audit reports could be issued by AFA to any company that subsequently to their performance require the audit report of an audited company. The preparation and issuance of the new audit reports are always subject to the written authorization of the related audited company and the signature of the contract according to the chapter 3.4 of this document.

The fee for these audits is established depending on the validity date of the report according to what is established in chapter 3.6. In the audits not included in annual packages, half of the audit fee will be distributed among all the original sponsors. The sponsor corresponding part will be stated as a down-payment for services.

3.7 Shelf-life of audit reports

Setting the validity of the reports is responsibility of audit sponsors. Nevertheless AFA establishes internal criteria for the audit management. The validity period is established assessing the following:

- Criticality of the product or services audited (according the criteria established in chapter 4.2
- Monoproduct or multiproduct plant
- Expected changes in short
- Result of the audit, identification of observations that could be considered deviations
- Action plan from the audited company

As a general rule for the critical products manufacturing or services, the maximum validity period is 3 years and for the non-critical 5 years.

4. AUDITS METHODOLOGY

4.1 Acceptance criteria

The acceptance criteria applied to audits will be established for each audit or group of audits of the same type, taking into account the following:

a) The supply criticality, as per the risk criteria described on point 4.2.

b) The specific requirements of each company and what it is established in the laws, regulations, guides, standards or recognized practices for each type of supply.

In cases where the above regulations not cover in an explicit way the operation object of the audit, AFA will look for the consensus standard in between their affiliates.

In a general way the reference used to set the acceptance criteria for the audits are as follows:

Type of audit	*Acceptance Criteria References*
Active Substances Manufacturing (APIs)	▸ Directive 2003/94/EC. EUGMP Part II ▸ CPMP, EMEA, ICH, FDA Guidelines ▸ EP, USP and JP
Excipients Manufacturing	▸ Directive 2003/94/EC. EUGMP Part II ▸ The Joint IPEC – PQG Good Manufacturing Practices Guide for pharmaceutical excipients 2006 ▸ CPMP, EMEA, ICH, FDA Guides ▸ EP, USP and JP
Packaging material manufacturing	▸ ISO 15378. Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP).
Finished and intermediate products manufacturing	▸ Directive 2003/94/EC. EUGMP Part I ▸ PIC'S Guidance ▸ PIC/S, CPMP, EMEA, ICH, FDA Guidelines ▸ EP, USP and JP
Computer System Design and Development	▸ Directive 2003/94/EC. EUGMP Annex 11 ▸ PIC/S Guides, GAMP Forum
Chemical and microbiological analysis	▸ Directive 2003/94/EC. EUGMP ▸ CPMP, EMEA, ICH, FDA Guides ▸ EP, USP and JP

Type of audit	Acceptance Criteria References
Logistics, warehouses and distributors	▸ Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011. ▸ WHO Good Distribution Practices (GDP) for pharmaceutical products (QAS/04.068/Rev2). ▸ Annex 2 Good trade and distribution practices for pharmaceutical starting materials (WHO) ▸ The IPEC Good Distribution Practices for Pharmaceutical Excipients (2006). ▸ Guía de bones pràctiques en el transport de medicaments (Direcció general de recursos sanitaris- Generalitat de Catalunya). ▸ Annex 9 Guide to good storage practices for pharmaceuticals- WHO (World Health Organization) Expert Committee on specifications for pharmaceutical preparations.

4.2 Criticality based on identified risks

The criticality of the supply will be always based on the ethic principle to guarantee the absence of risk to the patient. In order to ensure that the audit will follow this principle, the following aspects will be taken into account for each supply:

- Type of supply (excipient, active substance, contract laboratory, etc.).
- Function of the supply regarding the related GxP processes.
- Dosage form and administration route related to the supply.
- Activity/toxicity level or risks to the final product security or efficacy.
- Monoproduct or multiproduct plant.

The result of taking into consideration all these factors will determine the requirements required to the supplier during the audit.

4.3 Classification of observations

The audits are focused on reviewing and understanding the quality, management, manufacturing and control processes. Through this understanding, the compliance with the significant and applicable parts of the selected guidance is determined.

The observations identified are assessed to evaluate the risk for the patient, taking into consideration the environment where the deficiencies are produced.

Each deficiency identified is classified as Critical, Major, Minor and Recommendations, based on the following definitions:

- ***Critical.*** The deficiency introduces high and direct risk for the patient health (product's quality or safety) and mechanism to mitigate the risk are not in place. It is also critical any observation that entails fraud or falsification of products and data.
- ***Major.*** The deficiency involves a risk for the patient health (product's quality or safety) or a direct GMP principle noncompliance, but measures to mitigate the risk are in place
- ***Minor***. The deficiency involves a low risk for the patient health (product's quality or safety) or interpretable as a non-compliance of a GMP principle.
- ***Recommendation:*** Any item, practice, process, etc. that in the future could generate some problem, deficiency or GMP principle noncompliance is identified.

4.4 Execution of the audit

The execution of the audit entails the following steps:

1. **Signature of the CDA,** if needed.

2. **Establishment of the objectives and acceptance criteria** of the audit, taking into account the risk evaluation and the requirements of the audit sponsors. At this point the number of the needed audit days is established.

3. **Audit logistics arrangement.** Audit dates are fixed and the trip is planned.

4. **Preparation of the agenda and contact with the supplier.** The agenda is issued by the auditor taking into account the audit goals. AFA sends it to the supplier with enough time in advance to allow the audited company preparing it accordingly.

5. **Development of the audit.** The audit is divided in the following sequence:

    a) Presentation Meeting. Companies introduction and planning agreement

    b) Inspection of facilities, processes and related documentation

    c) Wrap-up meeting. Summary of the audit results, overall impressions, and observations

6. **Audit Report Preparation.** The auditor prepares the report in the time frame agreed with AFA. The report is electronically managed and is sent in draft version to the audit sponsors for their revision. Final report is digitally signed and it is sent to the audit sponsors at the end of the revision process.

7. **Audit summary for the audited company.** Summary of the report that content the conclusions and observations of the audit are prepared and it is sent to the audited company. When necessary, an action plan to remediate the deficiencies identified is requested.

4.5 Audit Follow-up

The audit process could identify observations related to GMP compliance. The audited company should pay attention to them, establishing an Action Plant for its resolution.

AFA's follow-up activities are described below:

- Action Plan request after sending the Audit Summary.
- Evaluation of suitability of Action Plan.
- Distribution of the Action Plan to the audit sponsors.
- Follow-up of the progress of the Action Plan (at least semi-annual).
- Updated Action Plan distribution to the sponsors.
- Follow-up audit when the audit validity expires, if the interest remains.

5. AUDIT REPORT

The audit report is the documentary support of the audit and consists of different parts described in the following subchapters.

5.1 Summary

It will summarize the activities performed during the audit, the company profile, a brief description of the Quality System, Facilities and Premises, personnel and materials flow and Quality Control laboratory. It will be also reported a summary of the strengths and weakness identified in the audited company.

5.2 Observations

The observations that could be considered deviations of the acceptation criteria identified on each system will be detailed and classified by applying the criteria described in section 4.3.

5.3 Audit Team

It will identify the names and positions of all the people involved in a relevant way on the audit development, concerning both the audited organization and the auditor team.

5.4 Company Information

The company information will highlight the aspects describing the audited company, the scope of its activity and the certification level they have.

Typical aspects of this section are: Name and address of the company, foundation year, number of employees, turnover, product portfolio, main markets, quality certifications, previous audit experience, etc.

5.5 Methodology

The methodology followed in the audit will be described, always according to what is established in this Protocol and the audit objectives.

5.6 General evaluation

In this section all the aspects that are common to all the products or services manufactured or provided are reported. Typically among others, the Quality Management and Organization, Buildings, facilities and equipment evaluation, personnel training, documentation system, materials management, general production management, quality control facilities and validation (cleaning, analytical method and processes, among others).

5.7 Specific part of the product or service

The content of this part is focused in the specific details of the products or services and the specific requirements from the audit sponsors. This part covers the concept of closed part established in chapter 3.1.

5.8 Conclusions

In this section an overall summary of the results is reported.

5.9 Additional documents

Copies of the relevant documentation collected during the audit are enclosed as well as the auditors' professional history and the declaration of conflict of interest.

6. FINAL EVALUATION OF THE SUPPLIER

The audit is part of the suppliers' validation process and therefore, it is an additional element to be considered when the final evaluation of the supplier suitability is performed.

The audit and the report, by themselves and in isolation, are not conclusive. However, they constitute an integral part of the suppliers' validation process.

The final evaluation of the supplier is a complex process requiring the integration of several laboratory-specific aspects that should be known and assessed.

Each company will decide in a private way about the supplier and supply suitability, taking into account its own policy of suppliers' approval / validation and the risk criteria associated to its own products.