Shared third party audit program

Contents

Authorization document	Author	Sales	Finance	Quality Assurance	Date effective
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Distribution	N/A				

1. General

According to the EU legislation the following is valid: *"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).

Both 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 also 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 (MAH) of their manufacturers or suppliers of the Active Pharmaceutical Ingredient (API) should be an integral part of the Supplier Qualification Procedure of the MAH.

Audits should be performed by qualified, trained and well experienced auditors. The audit should be properly documented and the audit reports will be subject to inspection by the Competent Authorities during inspections of the MAH 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, if necessary, other companies in the supply chain such as an intermediate company, an Agent, a Broker, a Packer, a Re-Packer, a Distributor or a Importer of the API.

A MAH can conduct audits herself or assign a Third Party to perform the audit.

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

Several options for performing an audit are acceptable for the European Authorities:

- A **Second Party Audit** of the API manufacturer performed by the Qualified Auditors of the MAH.
- A **Third Party Audit** of the API Manufacturer performed on behalf of the QP of the MAH. The QP of the MAH (Contract Giver) confirms that the Audit Process of the contract acceptor 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 QP ensures that the scope of the audit is applicable to each Medicinal Product that uses the API as Starting Material.

In the opinion of the *"Ad Hoc GMP Inspection Services meeting"* of EU Inspectors organized by EMA, it was decided that MAH should evaluate for themselves whether a possible conflict of interest could occur with any Third Party Audit option.

2. Scope

Description of the Laboratorium Ofichem B.V (Lab Ofichem) shared third party program.

3. Definitions and abbreviations

ASMF	Active Substance Master File
API	Active Pharmaceutical ingredient
DMF	Drug Master File
MAH	Manufacturing Authorization Holder
GMP	Good Manufacturing Process
QP	Qualified Person
EMA	European Medicine Agency
QA	Quality Assurance

4. Shared Third Party audit program

The approach performed by many Drug Product Manufacturers towards the legal requirement of auditing is to perform one to one audits of their API manufacturers. However, it is recognized that audits are time-consuming and expensive for both the API and Medicinal Product Manufacturer. There is a potential risk for significant audit overload (so called “audit fatigue”) in the Pharmaceutical Industry if this is the only option used. Consequently, it often appears that a Drug Product Manufacturer is not even welcome to perform an audit, especially if relative low quantities are purchased.

The aim of the Shared Third Party audit program of Laboratorium Ofichem BV (Lab Ofichem) is to provide a standardized (Shared) 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. Lab Ofichem operates as a contract audit organization in this matter (contract acceptor).

The audits within the framework of the Shared Third Party audit program are conducted by Lab Ofichems Certified Auditors. Standardized reports with classification of findings are issued.

Third Party Audits should be initiated by the MAH for the Medicinal product according the European directive 2001/83/EC and its amendments, in which it is defined that the MAH has the responsibility for assuring that the API is manufactured in accordance with the GMP in force.

In case several MAHs 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”.

There are several distinct advantages of shared audits:

1. For the API manufacturer. A joined audit for several customers will be performed at once, which is much more interesting for the API manufacturer than one to one audits.
   It saves time and the total quantity purchased by the number of customers is significantly lower then individually customer audit.
2. For the MAH. Performing audits is very time and cost consuming. Both can be saved in such an approach. Especially for the products that are not on the top of the priority list to be inspected.
3. For Lab Ofichem. In such a way an intensive partnership with both the API suppliers and the MAH can be build up and maintained.

All the audits reports, request for audits and any other information are kept strictly confidential. A more detailed description of the process of shared party audits by Lab Ofichem is given in Chapter 4.

The Lab Ofichem Auditing documentation provides the framework for the standardized audit program. Trained auditors follow the principles defined in the auditing guide, to ensure that the GMP status (ICH Q7) of each API manufacturer is assessed.

The audit report will include descriptions of all subjects covered during the audit. Objective evidence for GMP deficiencies observed during the audit will be included in the report and such deficiencies will be classified by the auditors (classification rating; see table 1).

Critical	A deficiency which has produced, or leads to a significant risk of producing, either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal. Examples: • Cross contamination; • Contaminants/microbiological contamination of sterile products; • Deviations/changes (with consequences that are harmful to health or life-threatening); • Contamination with serious medical consequences (solvents, pesticides); • Defect/deficiency that represents an offence requiring intervention by the authorities; • Significant deviations in the content of the quality documentation; • Iterated appearance of major deviations.
Major	A non-critical deficiency, which has produced or may produce a product, that does not comply with its marketing authorization; or which indicates a major deviation from EU Good Manufacturing Practice; or which indicates a failure to carry out satisfactory procedures for release of batches; 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. Examples: • Significant non-compliance with the GMP rules or significant deviations from the GMP Guidelines; • Inadequate discharge of the responsibilities of specialists from Quality Assurance; • Significant deviations of the product from the DMF/ASMF content and or prior set specifications; • Deviations that may result in residues that are harmful to health (Critical/Major, depending on the substance and therefore the risk).
Other	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). Examples: • Non-conformance to the GMP rules or deviations from the GMP Guidelines; • Deviations of production and testing from the DMF/ASMF; • Deviations and changes; • Missing documentation for processes proven to be correct.

Table 1: Classification of deficiencies.

5. Reassurance absence of Conflict of Interest

Ofichem group is split into two operations: API Production and trading. The production of API products covered by Lab Ofichem and trading activities are divided in Ofichem BV for veterinary and Ofipharma for human.

Ofichem BV is a trader known in the veterinary sector of the pharmaceutical industry. A Shared Third Party Audit program or a trader gene rally evokes the idea of a conflict of interest.

Ofichem BV is a known trader in the veterinary segment of the pharmaceutical industry. A Shared Third Party audit program of a trader generally evokes the idea of a conflict of interest.

In the pharmaceutical industry conflicts of interest are generally solved by a company structure with an independent QA department, whereas the general direction commits to respect the QA decisions.

Lab Ofichem is a European GMP certified API manufacturer with an independent QA department. This Shared Third Party audit program is part of the responsibility of the QA department of Lab Ofichem. As such the absence of a conflict of interest can be reassured.

Lab Ofichem is not interested in the gathering of approval reports to sell with the trading products of Ofichem. The structure of this shared third party audit program will not allow such practices. Lab Ofichem is interested in shared third party audits of the starting materials, while simultaneously the synergy between companies of the Ofichem-group provides the opportunity (knowledge of manufacturing APIs, awareness of many interested customers) to maintain a Shared Third Party audit program.

6. Contract structure

A third party auditing company is in essence a contract auditor, that is contracted by the MAH (as described in chapter 7 of the EU GMP guidance). Therefore Lab Ofichem acts as a contract acceptor. The QP/Responsible Person of the MAH is the contract giver. A standard contract is presented in annex 1.

Being a contract acceptor, all information about contract givers are handled strictly confidential. Information about participation is not shared with any other (participating) parties. The contract (see annex 1) includes this topic and ensures confidentiality.[1]

Lab Ofichem is willing to be inspected by all contract givers and by all (inter)national authorities, if necessary.

7. The auditor

An auditor is only qualified for performing the Shared Third Party audits if:

- the auditor has a particular educational background and/or experience, and
- the auditor is certified according to the APIC training course for auditors.

7.1. Educational Background and Experience

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

1 The auditee is not part of the contract (e.g. to ensure confidentiality), since the API manufacturers in China are commonly known to be reluctant to sign an English contract before the audit starts. With the API manufacturer a bi-lingual secrecy agreement between Lab Ofichem and auditee is used.

At least 5 years practical experience (relevant function) in manufacturing of Active Pharmaceutical Ingredients under GMP conditions may also be considered as sufficient knowledge and background.

The auditor must have a good knowledge of English Language, and preferably of the Chinese language.

7.2. Auditor Training Course for 'Certification'

Attendance at a specific five-day APIC training course (two and a half days related to GMP in API manufacturing and two and a half days for training in effective auditing techniques), including subsequent examinations is a requisite for becoming a Lab Ofichem Certified Auditor.

7.3. Responsibilities

The auditor operates under the direction of the Quality Assurance Department of Lab Ofichem and will therefore report to the Head of the department.

8. The auditing process

The Following Section describes the steps that are followed in the audit process from the initial contact until the distribution of the audit report and the follow up (see figure 1).

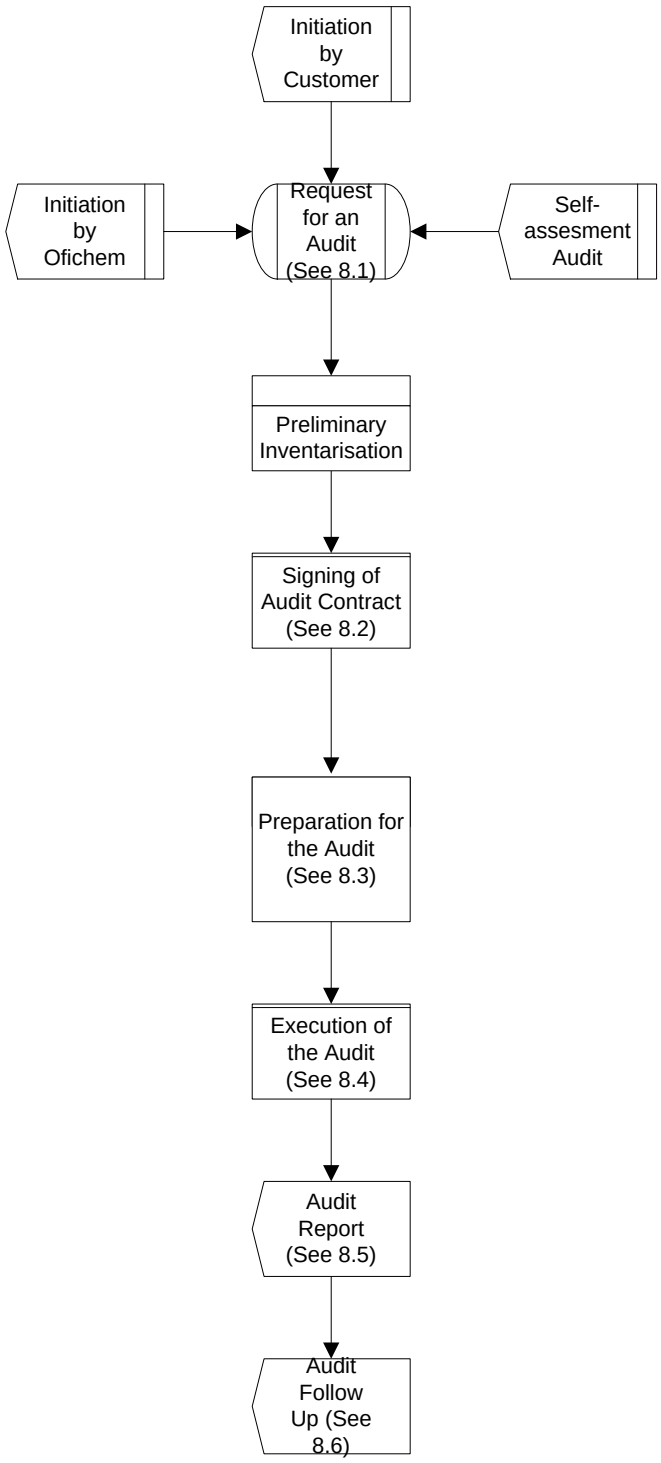

Figure 1: The auditing process.

8.1. Request for an audit

There are three possibilities for an audit request.

1. Initiation by Lab Ofichem
2. Initiation by one or more QP(s)/Responsible Person(s) of MAH(s)
3. Initiation for a self-assesment

A request to initiate an audit should be made to the Quality Assurance Department of Lab Ofichem

8.2. Preliminary Inventarisation

Preliminary to conducting an audit, Lab Ofichem will collect information and agree with each MAH on the following topics:

- Scope of the audit (EU GMP, US cGMP, oral, parenteral, etc.)
- Steps of the audit process
- Corrective Actions and Preventive Actions of previous audit
- Expected time inputs and expected costs
- Sample of an audit report, if desired
- Timetable

Next, Lab Ofichem will contact all other customers that purchased any API of the selected auditee the last 2 years. Lab Ofichem will send them a standardized letter. In this letter Lab Ofichem will ask the customers if they want to join the audit.

If any customer wants to join, Lab Ofichem will have the same preliminary inventarisation with that customer as with the original initiator.

Obviously, all information will be kept strictly confidential. Potentially interested MAHs, will not be aware if other MAHs or how many MAHs, are interested in conducting the audit.

8.3. Audit Contract

After the Preliminary inventarisation, Lab Ofichem will set up an audit contract (See annex 1). This audit contract has to be signed by the QP/Responsible Person of the MAHs and by the head of the QA department of Lab Ofichem. Contracts with each QP/Responsible Person will be documented separately.

8.4. Preparation of the audit

Initially the auditee is contacted and requested to provide relevant and available information for the audit (e.g. Site Master File, pre-audit questionnaire, etc.).

8.5. Execution of the audit

As a guideline, the audit will be performed by one auditor for two days. The customer has the responsibility to define the duration of the audit and the number of auditors if it is judged that more or less time or auditors are required to meet their requirements depending on the scope of the audit.

Before the audit, the customer(s) and the auditee will receive an audit plan from the auditor(s), 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 auditor) 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 relevant GMP guidelines.

All observations relating the GMP deficiencies will be explained, clarified and classified (see section 2 for the classification rating) during the final wrap up meeting with the Senior Management of the auditee.

8.6. The audit report

At the latest, within a period of one month after the audit, the auditor sends an audit report to the auditee. The audit report will include a management summary and an overview of which ICH topics were evaluated during the audit. The auditee should check the accuracy and respond to any observations, proposing corrective actions, responsibilities and time frames within one month.

The following data will be included in the report:

- The identity, registered address, manufacturing address, ownership and background information of the audited manufacturer;
- The identity and roles of key staff participating in the audit;
- The full contact details of the person through which the audit was arranged;
- The dates of the audit;
- The scope of the audit, including the stages of manufacture and the buildings audited;
- A list of all active substances directly included in the audit scope;
- Any activities that were not covered by the audit;
- The name and signature of the auditor;
- The dates of any previous audit conducted in the framework of Lab Ofichem's audit program. If any of the audits did not conclude with a positive GMP compliance status, a brief summary of the reasons for this should be recorded;
- A proposed re-assessment period;
- The high risk areas for audit specific to the site or products being audited. For example, these could include but not be limited to:

    - process, cleaning or validation;
    - risk of cross-contamination with other active substances or other substances;
    - potential for generation of unknown impurities;
    - risk of mix-up of materials and products through materials handling or packing;
    - change control;
    - deviation recording or management;
    - security sealing of active substance containers and security or temperature control of shipments.

Subsequent audits conducted as part of the ongoing supplier audit program may have a reduced scope focusing on the highest risk areas. In such cases the highest risk areas should be identified and justified.

On receipt of the audit report from the auditee, the auditor will review and confirm that a response with realistic timelines has been received for each observation, sign the audit report and make copy's for the auditee and the customer(s) within one month. The total process (audit, audit report, response auditee, evaluation auditor) will take approximately three months.

The original audit report remains valid for 3 years and will be digital archived for 5 years by Lab Ofichem.

The customer(s) has/have the responsibility to review the signed audit report and decide if deficiencies have been adequately addressed.

The evaluation of the impact of the audit deficiencies on the GMP status of the API(s) used in the Manufacture of Medicinal Products is the responsibility of the QP/Responsible Person of MAH(s).

8.7. Resolution of disagreement with GMP deficiencies or performance of the auditor

In case the QP/Responsible Person of the MAH is not satisfied with the Quality of the audit report or with the performance of the auditor, the QP/Responsible Person should contact Lab Ofichem in writing and explain their concerns. Lab Ofichem will review the concerns with the auditor and will try to come to a mutual satisfactory solution.

9. Audit Follow Up

Following completion and issue of the audit report, the auditee should issue periodic updates on progress with proposed actions to Lab Ofichem based on the timelines defined in the audit report.

Lab Ofichem will check if the proposed actions of the auditee in response to the audit observations have been implemented in a timely and effective manner.

Once in the three years Lab Ofichem will do a follow up audit including auditing of the effectiveness of the corrective actions defined in the original audit report. If Lab Ofichem is going to perform a follow up audit all customer(s) will be informed and preliminary inventarisation and the rest of the program will be started again.

10. Costs Considerations

The costs for participation depends partly on the amount of participators. The following aspects are considered:

- Audit, physical audit and preparation.
- Audit report and follow-up (CAPA review, etc.)
- Travelling expenses (based for audits in China) if audits are performed in another country the total prices will recalculated).

The costs for each participant are provided in table 2.

Table 2: Costs per audit, depending on the number of participants.

No. of participants	Costs	Comment
1	€3800,- *	On request 1 day audit €2300,-
2	€1900,-	
3	€1267,-	
>3	€ 950,-	

*: two days audit
In all cases the statutory value added tax will be added.

11. Other additional services

Lab Ofichem intends to maintain a database of worthy, compliant manufacturers, based on the information gathered with the presented Shared Third Party audit program.

On request, several other services can be provided (see table 3):

- Assistance with supplier selection;
- Assistance (organizing, accompanying, translating) to your companies second party audits;
- Third party audit of manufacturer of non-GMP raw materials or intermediates against appropriate standards (ISO 9001, ICH Q7);
- Third party audits of distributors, traders, brokers and re-labelers according to appropriate standards (GDP, ICH Q7);
- Third party audit (not shared) on the shortest term possible, in case of regulatory pressure.

	Manufacturer of non-GMP raw material	**Manufacturer of API intermediate**	**Manufacturer of finished API**	**Distributors**	**Marketing authorizatio n holder**
Major standards of compliance	ISO 9001	ICH-Q7 EU GMP (II)	ICH-Q7 EU GMP (II) ICH-Q1, 2, 3, 6, 9, 10, 11	GDP	EU GMP (I) or 21CFR210-1 ICH-Q1, 2, 3, 8, 9, 10
Common problems	(1)Inefficient implementation of ISO 9001 principles.	(1) Lack of awareness of requirement to comply with GMP; (2) Product insufficiently defined in terms of purity (3) Production moved or sub-contracted for economical or environmental reasons, without notification to customer.	(1) Gaps in GMP compliance; (2) Lack of awareness of ICH-Q2, Q3 & Q11 requirements; (3) Undecla-red sub-sourcing and repackaging of API.	(1) Lack of transparency; (2)Weak sourcing and monitoring of suppliers; (3) Repacka-ging of API from undeclared sources.	(1)Weak sourcing practice; (2) Cost and complexity of supplier audits.
What can be done	Including the key raw materials in the GMP audit of the API	Including the intermediate in the GMP audit of the API	Audit of GMP compliance and manufacturing capacity	GDP audit	**Sourcing services Auditing services**

Table 3: Potential opportunities and services.

12. Annex 1 Audit Contract

Agreement on Audit Execution and Secrecy

between **<name of company/MAH>** a company organized and existing pursuant to the laws of **<country company/MAH>**, having its principal place of business at **<address company/MAH>**, hereinafter referred to as "Customer"

and

Laboratorium Ofichem B.V. a company organized and existing pursuant to the laws of The Netherlands, having its principal place of business at Heembadweg 5, Ter Apel, The Netherlands, hereinafter referred to as "Lab Ofichem"

1. Subject of the Agreement
Lab Ofichem will conduct audits on behalf of the Customer, after mutual agreement on auditee(s), drug substance(s), duration, scope and costs of the audit.

The audits will be performed by a qualified and APIC certified auditor in order to verify the degree of compliance of the auditee with the ICH Q7 Guide "GMP for APIs".

2. The Audit
The audit date will be arranged between Lab Ofichem and the auditee. Any deficiencies found during the audit will be classified by the auditor and reported in the closing meeting of the audit.

3. Audit Report
The audit report prepared by the auditor will give objective evidence of any GMP deficiencies found during the audit and each deficiency will be classified. A digital copy of the audit report will be sent to the auditee no later than one month after completion of the audit. The auditee is asked to check on accuracy and respond to any deficiencies within one month. The auditor will review and confirm that a response with realistic timelines is received for each observation.

The final digital audit report will contain all classified deficiencies and all proposed actions of the auditee. As such, it will provide a detailed overview of the state of compliance of the auditee. The final audit report will contain a clear documented statement e.g. an audit summary should be available indicating that the API manufacturer is acceptable or not as a supplier. This statement can be used by the QP as a basis for his decision for filing a QP declaration.

Within three months and after receiving of the payments a signed digital copy of the audit report is provided to the Customer . The original audit report will be archived by Lab Ofichem for 5 years. The auditor will retain the auditing notes during the same period.

4. Audit Follow Up
The Customer is responsible to review the audit report including the proposed actions of the auditee. In case the proposed actions of the auditee are not considered to be sufficient by the Customer, the auditor will communicate this to the auditee and keep the Customer informed about follow up.

The Customer is responsible for the final conclusion about approval or rejection of the auditee.

5. Confidentiality
Lab Ofichem undertakes not to disclose any specific information related to the Customer.

The audit report and other formal correspondence related to the audit execution is confidential. The Customer and Lab Ofichem agree that this confidential information is treated in the utmost and strictest confidence and assures that none of such confidential information is brought to the attention of third parties, unless both parties agree to share the information.

The Customer agrees not to use the confidential information for activities that are in competition with the activities of the auditee(s).

Lab Ofichem will maintain a secrecy agreement with the auditee. The Customer acknowledges that the confidential information may possess a special, unique and extraordinary character that would not be adequately compensated by money. The Customer agrees that in the event of use of the information in breach of its obligation in addition to legal and equitable rights and remedies, Lab Ofichem shall have the right to obtain temporary or permanent injunctions against such prohibited disclosure or use.

6. Liability
1. Lab Ofichem shall be held liable in causes to the Customer during the implementation of the Agreement only to the extent that they are the result of gross negligence. In case that Lab Ofichem shall be held liable the extent is limited to the costs of the audit(s).
2. Lab Ofichem shall not be held liable for claims by the Customer regarding insufficient performance by the Auditor.
3. Lab Ofichem shall not be held liable for unsuccessful inspections by authorities after having been audited under this agreement.
4. Lab Ofichem shall not be held liable in the case where participating companies are taking measures leading to any kind of financial impact on the Customer.

7. Copyright
The copyright of the audit report will be shared by Lab Ofichem and the Customer. Any requests to pass on the audit report to subsequent Third Parties should be made to the other party. Written agreement will be required from the other party before the audit report may be issued to a subsequent third party. Copies of the audit report may be shown on request to European Member State Inspectors during inspection of the Medicinal Product Manufacturers.

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

9. Legal venue and applicable law
Legal venue for any disputes shall be Ter Apel. The laws of the Netherlands are applicable.

10. 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.

11. General Terms and conditions of delivery of Laboratorium Ofichem B.V.
The General Terms and Conditions of Delivery shall apply to all offers made, agreements concluded or actions performed by Laboratorium Ofichem BV. The payment conditions is 30 days instead of 14 days”General terms and conditons of delivery of Laboratorium Ofichem B.V.

12. Term
This agreement shall come into force at the latest date of signing.

The present agreement may be terminated upon written notice by one of the parties. The obligations under the section of confidentiality of this agreement shall remain in effect for ten (10) years from the date thereof.

_____
Place, date and signature of the Customer

_____
Place, date and signature of Lab Ofichem

Appendix:
General Terms and Conditions of Delivery shall apply to all offers made, agreements concluded or actions performed by Laboratorium Ofichem BV.