TITLE:

SPECIFIC CRITERIA FOR THE INSPECTION OF MULTI-SITE STUDIES

SUMMARY: This document interprets the Principles of Good Laboratory Practice that the Argentine Accreditation Body (OAA) applies in relation to the studies carried out in more than one site (multi-site study)

This document is a translation from CE-BPL-02 version 1 issued in Spanish.

CONTENTS

1. OBJECTIVE

The specific criteria for the inspection of multi-site studies applied by the Argentine Accreditation Body (OAA) for monitoring Good Laboratory Practice (GLP) are an interpretation of the OECD Principles of Good Laboratory Practice that test facilities must meet.

2. SCOPE

This document is applicable to any test facilities that perform multi-site studies and request the recognition of its compliance with Good Laboratory Practice (GLP) as well as to the inspectors and technical experts who participate in inspections, study audits, re-inspections, follow-ups and special inspections.

3. REFERENCE DOCUMENTATION

- **ENV/MC/ CHEM (98)17** "OECD Principles of Good Laboratory Practice" (Document No. 1 issued by the Environment Directorate of the Organization for Economic Co-operation and Development - OECD).

4. ABBREVIATIONS AND DEFINITIONS

4.1. ABBREVIATIONS

- GLP: Good Laboratory Practice
- OAA: Argentine Accreditation Body
- OECD: Organization for Economic Co-operation and Development
- SD: Study Director
- PI: Principal Investigator
- QA: Quality Assurance

4.2. DEFINITIONS

The definitions given in the current versions of ENV/MC/ CHEM (98)17 "OECD Principles of Good Laboratory Practice" (Document No. 1 issued by the Environment Directorate of the Organization for Economic Co-operation and Development - OECD) and of the *"Program for Good Laboratory Practice Monitoring",* PRO-BPL, apply.

5. RESPONSIBILITIES

The responsibilities are described in clause 6.

6. DESCRIPTION

The requirements with regard to which the OAA recognizes GLP compliance of a test facility that requests this recognition are based on the Principles of OECD Good Laboratory Practice (Document No. 1 issued by the Environment Directorate of the

Organization for Economic Co-operation and Development – OECD). These Principles must be implemented by test facilities that carry out non-clinical safety studies in order to obtain data on their proprieties and/or their safety regarding human health and/or the environment and to submit these data to the Regulatory Authority for the purpose of registering or authorizing the marketing of pharmaceuticals, pesticides, cosmetic products, veterinary drug products, food and feed additives and industrial chemicals.

The OAA monitors non-clinical safety tests of pesticides and industrial chemicals carried out in the laboratory, in greenhouses or in the field.

The interpretations of the GLP Principles (OECD) provided by the OAA to monitor the compliance of test facilities that carry out studies in more than one site, either belonging to the same test facility or that are subcontracted by it, are detailed below.

The numbers and titles in bold relate to the requirements of the Good Laboratory Practice Principles. Only the text of the clause for which a criterion is set out is included.

OAA's criteria are identified by the letter C and the number of the Good Laboratory Practice Principle.

Development:

Principles of Good Laboratory Practice

1. Test facility Organization and Personnel

1.1 Test Facility Management's Responsibilities
1.1.2.
h)- ***ensure, in the event of a multi-site study, that, if needed, a Principal Investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented;***

o)- ***ensure for a multi-site study that clear lines of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Program(s) and study personnel;***

C 1.1.2 h) and o) - The mechanism of communication among the parties involved in the study must be agreed and documented before the study is launched.

The following situations may occur:

Case 1- Phases of a study are carried out in more than one site, where all the sites are under the management of the test facility that is in compliance with the GLP or that has requested the monitoring to demonstrate its compliance, i.e. a multi-site study is created within a single test facility. The management must then appoint in each site, other than the Study Director's domicile, a Principal Investigator who is

part of the same test facility and informs the SD about the phase delegated to him/her.

Case 2- A Multi-site study, where the test facility subcontracts the performance of some phases of a study to one or more sites that are under a management different from the management of the test facility that complies with the GLP or that has requested the monitoring in order to demonstrate its compliance, where the SD resides.

1.2 Study Director's Responsibilities

1.2.2 d)- ***ensure that the study plan and the final report for a multi-site study identify and define the role of any Principal Investigator(s) and any test facilities and test sites involved in the conduct of the study;***

C 1.2.2 d)

For case 1- The plan must reflect this situation, indicating PI's address, phases of the study that are delegated and responsibilities. The PI may forward his/her report to the SD for its inclusion in the final report or may send directly his/her comments and raw data to the SD who will prepare the report.

For case 2- The plan must reflect this situation, indicating PI's address, phases of the study that are delegated and responsibilities.
The PI could work according to the study plan developed by the SD regarding the phase that has been delegated or could develop his/her own study plan for this phase. In the latter case, he/she shall have information from the SD related to the original study plan, in particular regarding the phases under his/her responsibility.

1.3 Principal Investigator's Responsibilities

The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice.

C 1.3

For case 1 When the PI just submits his/her comments and raw data to the SD for the SD to develop the report, these contributions must be accompanied by a written statement of the PI related to the GLP compliance of the phase that has been delegated to him/her.

For cases 1 and 2 – The report signed by the PI that is submitted to the SD must contain the compliance statement made by him/her related to the delegated phase.

2. Quality Assurance Program

2.1. General

2.2. Responsibilities of the Quality Assurance Personnel.

2.2.1.e) ***promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable;***

C 2.2.1 e)
For case 1-
I) There is only one Quality Assurance Unit responsible for carrying out, in all the sites, inspections, audits and the provision of reports to the management, the SD and the PI.
II) There is only a Lead Quality Assurance Unit, responsible for quality assurance of the multi-site study, which is located where the SD resides. In addition, each site to which a phase has been delegated has its own Quality Assurance Unit responsible for carrying out, in its own site, inspections and audits and for reporting to the Lead QA Unit and to the PI the outcome of these audits.

For case 2 – Quality Assurance in every site of a multi-site study is the responsibility of the management and the Quality Assurance Unit of the test facility where the SD operates.
I) The inspections and audits are carried out by the Quality Assurance Unit of the contractor.
II) The inspections and audits of the delegated phases could be assigned to the Quality Assurance Unit of the outsourced site. This delegation must be documented and accepted by the parties.

For either of the two situations described above (I and II), the mechanism for reporting the results of the inspections and audits performed on the delegated phases to the PI, QA, SD and the managements of the Contractor and the Subcontractor, must be clearly documented.

f*)- prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data*

C 2.2.1 f)
For Case 1-
I) The Quality Assurance statement covers the whole study, describes the inspections carried out and ensures that the final report contains the totality of the raw data obtained in all *the sites*.
II) If the SD encloses IPs' reports, the "secondary" statements of the QA units should be enclosed. However, if the SD only receives raw data or uses IPs' report as raw data for his/her own report, the "secondary" statements of the QA units would not be

justified and the Lead QA could provide a complete and single statement covering all the study phases.

For case 2-

Lead Quality Assurance should enclose in the final report the statements of each QA unit of each site.

6. Test and Reference Items

6.1 Receipt, Handling, Sampling and Storage

2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.

C 6.1.2

Maintaining the integrity/ stability during transportation is essential, so the use of a reliable means of transportation and custody chain is critical. When test items of different studies are transported between sites on a consignment, it is essential that an adequate separation and identification exist to avoid mix-ups or cross contamination. Procedures should be established to preserve their integrity.

7. Standard Operating Procedures

7.1 ***A test facility should have written Standard Operating Procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to Standard Operating Procedures should be approved by test facility management***.

C 7.1 The following are some examples of specific procedures for multi-site studies:

- Selection and monitoring of test sites.
- Appointment and replacement of Principal Investigators.
- Transfer of data, specimens and items among sites.
- Storage, devolution or disposition of test and reference items used in remote testing sites.

8.0. Performance of the Study

8.1*. Study Plan*

1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section 2.2.1.b., above.

The study plan should also be approved by the test facility management and the sponsor, if required by national regulation or legislation in the country where the study is being performed.

C 8.1.1 A single study plan should be issued for each multi-site study.

8.2. Content of the Study Plan

8.3. Conduct of the Study

9. Reporting of Study Results

9.1. General

1. A final report should be prepared for each study. In the case of short term studies, a standardized final report accompanied by a study specific extension may be prepared.

C 9.1.1 A single final report should be issued for each multi-site study. The final report should include data from all phases of the study. It could be useful for the PIs to prepare a signed and dated report of the phase that has been delegated to them for its inclusion in the final report.
Such reports should include evidence that appropriate monitoring by quality assurance was carried out in this test site and contain enough comments to enable the SD to write a valid final report covering the full study.
On the other hand, the original data (raw data) could be transferred from the test site to the SD who should ensure that the data are included in the final report. A final report developed in this way should identify the PI(s) and the phase(s) for which they were responsible.

3. The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these Principles of Good Laboratory Practice should be indicated.

C 9.1.3 If the subcontracted entity has not been monitored and declared in compliance with the GLP by the OAA or if it is a test facility (national or international) in compliance with GLP recognized by the OAA (e.g. inspected by Authorities of Member Countries or Full Adherents), the phase(s) carried out by this facility shall be expressly excluded from the statement of compliance of the SD, indicating that these phases were not carried out according to GLP Principles.

9.2. Content of the Final Report

4. *Statement*

A Quality Assurance Program statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

C 9.2.4: See C 2.2.1 f)

7. *Storage*
The location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

C 9.2.7 The final report must identify the place where the study plan, test and reference items, specimens, raw data and the final report are stored. The reports produced by the Principal Investigators should provide information concerning the archiving of the materials for which they were responsible.

10. Storage and Retention of Records and Materials

7. RELATED DOCUMENTATION

ENV/JM/MONO(2002)9- OECD Series on Principles of Good Laboratory Practice And Compliance Monitoring. Document No. 13 Consensus Document of the Working Group on Good Laboratory Practice “The Application of the OECD Principles of GLP to the Organization and Management of Multi-Site Studies”.