

Unclassified

ENV/JM/MONO(2014)30

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

15-Dec-2014

English - Or. English

**ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

Cancels & replaces the same document of 26 September 2014

**OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE
MONITORING
Number 16**

**Advisory Document of the Working Group on Good Laboratory Practice -
Guidance on the GLP Requirements for Peer Review of Histopathology**

JT03368596

Complete document available on OLIS in its original format

This document and any map included herein are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.



ENV/JM/MONO(2014)30
Unclassified

English - Or. English

OECD Environment, Health and Safety Publications

**Series on Principles of Good Laboratory Practice
and Compliance Monitoring**

No. 16

**Advisory Document of the Working Group on Good
Laboratory Practice**

**Guidance on the GLP Requirements for Peer Review of
Histopathology**

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2014 ALSO PUBLISHED IN THE SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

- *No. 1, OECD Principles of Good Laboratory Practice (as revised in 1997)*
- *No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)*
- *No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)*
- *No. 4, Quality Assurance and GLP (as revised in 1999)*
- *No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)*
- *No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)*
- *No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)*
- *No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)*
- *No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)*
- *No. 10, The Application of the Principles of GLP to Computerised Systems (1995)*
- *No. 11, The Role and Responsibilities of the Sponsor in the Application of the principles of GLP (1998)*
- *No. 12, Requesting and Carrying Out Inspections and Study Audits in Another Country (2000)*
- *No. 13, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (2002)*
- *No. 14, The Application of the Principles of GLP to in vitro studies (2004)*
- *No. 15, Establishment and Control of Archives that Operate in Compliance with the Principles of GLP (2007)*

© OECD 2014 Applications for permission to reproduce or translate all or part of this material should be made to: Head of Publications Service, OECD, 2 rue André-Pascal, 75775 Paris Cedex 16, France.

ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in 11 different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/ehs/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organisations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

**For this and many other Environment,
Health and Safety publications, consult the OECD's
World Wide Web site (www.oecd.org/ehs/)**

or contact:

**OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

FOREWORD

The OECD Working Group on Good Laboratory Practice, at its 24th meeting in 2010, established a drafting group under the leadership of the UK (Dr. Andrew Gray) to prepare a guidance document on how pathology peer reviews should be planned, conducted and reported under GLP. The drafting group included representatives from the UK, Canada, France, Japan (medical products), Sweden, Switzerland, and the US (FDA and EPA). The Working Group agreed key stakeholders in industry should also be consulted during the development of the document. The stakeholders were identified by the members of the drafting group, and included representatives from trade associations, expert societies, large pharmaceutical companies and independent pathologists.

Drafts of the document prepared by the drafting group were circulated to the key stakeholders and Working Group for input. The 28th meeting endorsed the final version in April, 2014.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

1. Background

- 1.1. The histopathological assessment of tissue samples is one of the key endpoints of a toxicology study, and the results obtained will contribute substantially to the outcome and conclusions of the study.
- 1.2. Because the assessment of tissue specimens is based upon the expert opinion of the slide reading pathologist, it is common for test facilities to have implemented a peer review process whereby a number of slides are assessed by a second pathologist. The process is a means of assuring the quality and the accuracy of interpretation and maintaining best practices. Although there is no absolute requirement in the GLP principles to conduct peer review, most receiving authorities expect that some level of peer review will be performed. This document is concerned with the processes used to organise, perform and record the results of this review.
- 1.3. The peer review process can lead to changes in the interpretation of the slides and the reported results, and potentially the outcome and conclusions of the study. The purpose of this document is to provide guidance to pathologists, test facility management, study directors and quality assurance personnel on how the peer review of histopathology should be planned, managed, documented and reported in order to meet GLP expectations and requirements. This document is a complement to the guidance provided in section 3.6.3.7 of OECD Guidance Document 116¹, whose focus is on how histopathology peer review should be conducted.
- 1.4. There may be particular studies where the study sponsor requires that some or all of the slides are reviewed by a specific peer reviewing pathologist. This may be because the reviewing pathologist is an established expert in a particular field of pathophysiology, or has particular experience of the physiological affects of the test item under investigation. This approach allows for consistency of finding terminology and interpretation throughout different studies which are investigating the effects of the same test item. It is acknowledged that relevant experts are not always employed by a GLP facility and consequently it may not always be possible to perform the peer review in a GLP compliant facility.

2. GLP Requirements

- 2.1. Any requirements for peer review performed at the test facility or by external consultants, should be clearly described in the study plan or subsequent study plan amendments. This should include information on how the pathology peer review will be planned, managed, documented and reported. It should also be stated whether the review will be performed contemporaneously or retrospectively. If some or all of the above information is documented in an SOP a reference to the current version of the SOP would be acceptable.

¹ ¹ *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453.*

- 2.2. The study plan or subsequent amendments should provide an appropriate level of information to allow reconstruction of how tissues will be selected for peer review whilst allowing sufficient flexibility to react to unexpected pathology findings.
- 2.3. If the pathologist that is appointed to perform the peer review is located at a site geographically remote from the site where the study was performed there is no requirement for them to be formally appointed as a principal investigator. Because the reviewing pathologist is interpreting data and not generating data it would be appropriate for them to be considered as a contributing scientist. The study director maintains ultimate responsibility for ensuring that the peer review process is conducted in accordance with the principles of GLP (see bullets 3.1-3.3).
- 2.4. Details of how the peer review was conducted should be documented and retained within the study file. These activities will include information on the identity of the tissues that were reviewed, when the tissues were reviewed and by whom. Notes made by the peer review pathologist which are used to record observations during the histopathological examination of individual slides do not normally have to be retained in the study file.
- 2.5. All correspondence regarding the histopathological evaluation of the slides used for peer review between the sponsor and representatives of the test facility and the peer review pathologist should be retained in the study file, including minutes of teleconferences between the sponsor and the test facility.
- 2.6. For the purpose of reconstruction, raw data is defined as the documentation described in bullet 2.4 and 2.5. The original histology slides that are assessed by the reviewing pathologist are derived from the test system and meet the definition of specimens. However, the slides and corresponding blocks are needed for the reconstruction of the histopathology portion of the study and consequently must be archived for the same duration as the raw data.
- 2.7. If the peer reviewing pathologist does not concur with all or some of the conclusions drawn by the original pathologist a clear, transparent and unbiased process should be implemented to resolve their differences. This process should be documented within the facility's SOPs or procedures.
- 2.8. Where the peer reviewing pathologist's findings were significantly different from the original interpretation of the study pathologist, a description of how differences of interpretation were handled and changes made to the study pathologist's original interpretation should be discussed in the final report.
- 2.9. If, despite following procedures designed to resolve any differences of opinion, agreement cannot be reached then an independent expert or panel of experts may be used to resolve the issue. The conclusions of the panel should be clearly documented in the final report.
- 2.10. In most cases where there are no significant differences of opinion it will not be necessary to report in detail the outcome of the peer review in the pathology report or the final report. A simple statement that it was conducted and that the pathology report presents the agreed findings would usually suffice.
- 2.11. There is no requirement for the peer reviewing pathologist to sign the pathology report or the final report. However, in the absence of a signature there is an expectation that the peer

reviewing pathologist will sign the statement described in section 2.10. This statement should be retained in the study file.

- 2.12. The identity and affiliation of the peer reviewing pathologist should be listed in the final report.

3. GLP Compliance of Peer Review

- 3.1. The peer review process can lead to changes in the interpretation of histopathology findings that in turn may influence the outcome and conclusion of the study. Consequently, there is an expectation that the peer review should be conducted in compliance with GLP. However, it is recognised that for the peer review to be of scientific value it has to be conducted by a person with the appropriate specialist experience and expertise; consequently that may necessitate the use of acknowledged experts in particular fields who do not work within a GLP test facility. When a decision is made to perform pathology peer review in a non GLP facility it should be justified and recorded within the study plan and final report. Alternatively consideration should be given to whether it would be more appropriate for the pathologist who conducts the peer review to perform their review at the test facility that conducted the study. This would remove the need to transfer histopathology slides from one site to another and would also allow the peer reviewing pathologist to perform their work under the umbrella of an established GLP quality system. In such circumstances there is an expectation that the peer reviewing pathologist would receive an appropriate level of training in the relevant facility procedures.
- 3.2. The study director will be making a statement concerning the extent to which their study complies with GLP. If electing to utilise a non-GLP organisation for peer review the study director needs to be satisfied that the peer review process is sufficiently well managed, and that peer review data is of adequate quality. Key elements to consider include, but are not necessarily limited to:
 - 3.2.1. Evidence of experience/expertise of the reviewing pathologist.
 - 3.2.2. A review of the facility's SOPs or a documented agreement that the peer reviewing pathologist will use the test facilities SOPs and procedures.
 - 3.2.3. Chain of custody of samples and associated paperwork.
 - 3.2.4. Security of samples and documents whilst at the peer reviewing pathologists facility
 - 3.2.5. Validation of any computer applications (if applicable).
 - 3.2.6. Adequate quality assurance activities which may include an audit of the premises and equipment used by the reviewing pathologist.
- 3.3. If the peer review has been conducted in a non-GLP facility then this should be documented within the study director's statement.

4. Summary of Expectations

- 4.1. Peer review of histopathology is an important part of the process which ensures the quality of the interpretation of study results and can have a significant impact on the study outcome. It is therefore essential that peer review procedures are planned, conducted, documented and reported such that the integrity of the regulatory study is not compromised and activities can be fully reconstructed and verified.
 - 4.1.1. Histopathology peer review activities should be described within the study plan or subsequent amendments.
 - 4.1.2. Documentation of the peer review should describe the tissues and documents examined by the peer review pathologist. Reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and of the opinions expressed.
 - 4.1.3. There should be documented procedures that describe how any differences of opinion will be resolved.
 - 4.1.4. Any differences of interpretation that result in a significant change of the study pathologist's original interpretation should be discussed in the final report.
 - 4.1.5. The identity and affiliation of the peer reviewing pathologist should be clearly stated in the final report.