B-01

PFSB Notification 1226 No.6
December 26, 2013

Director-General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

# Guidelines for the Conduct of Laboratory Inspections under the Principles for Test Facilities Conducting Tests of New Chemical Substances

The Principles for Test Facilities Conducting Tests of New Chemical Substances (hereinafter referred to as the "GLP for Chemical Substances") are specified in "Principles for Test Facilities Conducting Tests of New Chemical Substances" (Notification in the joint names of the Director General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Director General, Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry, and Director General, Environmental Health Department, Ministry of the Environment under Notification 0331 No. 8 of Pharmaceutical and Food Safety Bureau (PFSB), 23.03.29 Notification No. 6 of Manufacturing Industries Bureau (MIB), and Notification No. 110331010 of Environmental Health Department (EHD), dated March 31, 2012, and the procedures, etc. for the conduct of laboratory inspections of test facilities governed by the GLP for Chemical Substances referred to in the notification in those joint names are specified in "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (Notification in the joint names of the Director General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Director General, Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry, and Director General, Environmental Health Department, Ministry of the Environment under PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7 and EHD Notification No. 110331011, dated March 31, 2011; hereinafter referred to as the "Notification of the Handling of Test Results"), and "Guidelines for the Conduct of Laboratory Inspections under the GLP for Chemical Substances" attached as an Appendix to "Guidelines for the Conduct of Laboratory Inspections under the Principles for Test Facilities Conducting Tests of New Chemical Substances" (Director General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Notification 0229 No. 2, dated February 29, 2012; hereinafter referred to as "Old Notification of the Guidelines for the Conduct of Laboratory Inspections").

Based on the results and other factors of GLP-based on-site examinations by OECD received by the GLP for Chemical Substances authorities in 2012, the "Guidelines for the Conduct of Laboratory Inspections under the GLP for Chemical Substances" is hereby established.

For the avoidance of doubt, the Old Notification of the Guidelines for the Conduct of Laboratory Inspections" is abolished effective as of December 26, 2013.

Appendix

Guidelines for the Conduct of Laboratory Inspections under the GLP for Chemical Substances

1 Purpose

In order to check the quality of study results used as materials for the examinations under Article 4 (including the cases where it is applied mutatis mutandis pursuant to Article 7) and Article 5 of the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973; hereinafter referred to as the "Act"), results of tests of the properties of the priority assessment chemical substance under Article 10, paragraph (2) of the Act, and results of tests of hazardous properties under Article 10, paragraph (2) and Article 14, paragraph (1) of the Act (hereinafter referred to as "study results"), or in order to verity the compliance of test facilities that conducted the studies subject to verification with the GLP for Chemical Substances pursuant to the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "Notification of the Handling of Study Results," the purpose of these Guidelines is to set forth detailed rules for laboratory inspections of those test facilities to be conducted by persons designated by the Director General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, as well as for the procedures associated therewith.

2 Scope of Test Facilities subject to Inspection

Inspections to be conducted under these Guidelines cover the test facilities that conducted studies to which the GLP for Chemical Substances applies (hereinafter referred to as "tests governed by the GLP for Chemical Substances") (hereinafter referred to as "test facilities governed by the GLP for Chemical Substances"). More specifically, these Guidelines cover the test facilities listed below:

(1) test facilities that belong to a person who gives a notification of manufacture, import or export of new chemical substances under Article 3 or 7 of the Act, a person who submits results of a test of properties of the priority assessment chemical substance under Article 10, paragraph (1) of the Act, or a person who submits a report on results of a study on the hazardous properties of the priority assessment chemical substance or monitoring chemical substance under Article 10, paragraph (2) or Article 14, paragraph (1) of the Act (hereinafter referred to as a "notifier, etc."), and that conducted the tests governed by the GLP for Chemical Substances;

(2) test facilities that conducted the tests governed by the GLP for Chemical Substances under an entrustment of a notifier, etc. (including universities, medical institutions and other research laboratories, and test facilities, etc. that belong to a foreign new chemical substance manufacturer that provided such notifier, etc. with test results to be attached to a notification, etc.); and

(3) test facilities for which a person who submitted an application for verification to the Director General of the Pharmaceutical and Food Safety Bureau under the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "Notification of the Handling of Test Results" (hereinafter referred to as an "applicant for verification").

3 Officials in Charge of Inspections

Inspections shall be conducted by an inspection team consisting of officials of the Pharmaceutical and Food Safety Bureau and, as necessary, officials of National Institute of Health Sciences. Whenever necessary, other scientists may be added to an inspection team.

4 Conduct of Inspections

Inspections shall be conducted, in principle, in either of the following (1) or (2):

(1) When test results are generated based on the tests governed by the GLP for Chemical Substances and, in principle, fall under any of the following:

(i) no inspection is conducted for the test facility governed by the GLP for Chemical Substances pursuant to these Guidelines within the past three years from the date on which the study director signs or seals the test results (hereinafter referred to simply as "test results") submitted in the notification or report specified in paragraph 2(1);

(ii) inspections were conducted for the test facility governed by the GLP for Chemical Substances to which the relevant test results pertain pursuant to these Guidelines within the past three years from the date on which the study director signed or sealed the test results, and the evaluation of the relevant test facility was Fail as set forth in paragraph 7-2) of these Guidelines; or

(iii) Director General of the Pharmaceutical and Food Safety Bureau finds it necessary to conduct inspections of the test facility governed by the GLP for Chemical Substances to which the test results pertains by reason of there being any doubt about the quality of those test results.

(2) When an application for verification is submitted to the Director General of the Pharmaceutical and Food Safety Bureau pursuant to the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "Notification of the Handling of Test Results," and Director General of the Pharmaceutical and Food Safety Bureau finds it necessary to conduct verification for the relevant test facility.

5 Procedures for Inspections

Inspections should be conducted in accordance with the following procedures:

1) Notice of the conduct of inspections to the notifier, etc. or applicant for verification

When the Director General of the Pharmaceutical and Food Safety Bureau finds it necessary to conduct inspections under paragraph 4 of these Guidelines, the Director General will give notice thereof to the notifier, etc. in Form No. 1 attached hereto and the applicant for verification in Form No. 2 attached hereto, respectively.

2) Details of Inspections

(1) Inspections should be conducted for the following matters:

(i) verification of the status of compliance with the GLP for Chemical Substances with respect to the equipment of the test facility subject to inspection and their operation and management; and

(ii) verification of the status of compliance with the GLP for Chemical Substances with respect to tests subject to inspection.

(2) Inspections should be conducted, in principle, under the following procedures:
(i) identification of the whole operation and management of the test facility;
(ii) patrol inspection of the test facility, and confirmation of the status of maintenance of equipment and apparatus;
(iii) entry into the test work sites;
(iv) confirmation of the storage status of the study plans, standard operating procedures, final reports, and other documents, raw data, specimens, etc.;
(v) confirmation of the activities of the quality assurance unit personnel; and
(vi) inspections and comparisons of raw data, specimens, final reports, etc. related to the studies subject to inspection.

(3) When it is deemed necessary as a result of inspections, submissions of samples, specimens, raw data, and other materials related to the test and other substances should be requested.

(4) After the completion of inspections, inspectors should point out any problems, when necessary, to the subject test facility on the spot. For clarity, categorization and measures of official guidance or instructions should be notified after the meeting of the GLP Evaluation Committee.

6 Reporting of Inspection Results

Inspectors should prepare a report on results of inspections under the GLP for Chemical Substances including the following items, and submit it to the Director General of the Pharmaceutical and Food Safety Bureau:

(i) summary of the content of the report;
(ii) brief description of the conduct of inspections;
(iii) results of inspections;
(iv) queries pointed out at the time of inspections, and answers of the test facility to those queries;
(v) draft judgment; and
(vi) other necessary matters.

7 Evaluation of Inspection Results

1) GLP Evaluation Committee

(i) The GLP Evaluation Committee will, upon request of the Director General of the Pharmaceutical and Food Safety Bureau, evaluate the status of compliance with the GLP for Chemical Substances by the test facilities subject to inspection and studies subject to inspection based on the report on results of inspections under the GLP for Chemical Substances prepared by inspectors.

(ii) The GLP Evaluation Committee consists of officials of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare and National Institute of Health Sciences, and other scientists.

2) Categorization of the Status of Compliance with the GLP for Chemical Substances

The GLP Evaluation Committee will comprehensively judge the status of compliance of test facilities subject to inspection with the GLP for Chemical Substances based on results of inspections of the test facility and tests subject to inspection, and evaluate either of which the

test facility should be categorized into:

Pass: It can be found that the test facility is compliant with the GLP for Chemical Substances, or that parts of the test facility are non-compliant with the GLP for Chemical Substance but corrective measures have been taken for those parts or the extent of impact of those parts on the quality of the tests is permissible.

Fail: It can be found that the test facility is fully or partially non-compliant with the GLP for Chemical Substances and the quality of the tests governed by the GLP for Chemical Substances conducted by it has been impaired.

3) Explanations about the circumstances by the notifier, etc. or applicant for verification with respect to results of inspections

(1) When it is determined as a result of deliberations at the meeting of the GLP Evaluation Committee that the facility subject to inspection and the tests subject to inspection are fully or partially non-compliant with the GLP for Chemical Substance, those parts that are non-compliant with the GLP for Chemical Substances will be indicated to the notifier, etc. or applicant for verification through Office of Chemical Safety, Pharmaceutical Evaluation Division, Pharmaceutical and Food Safety Bureau.

(2) With respect to the matters presented in (1) above, the notifier, etc. (including the interested parties of the test facility subject to inspection) or applicant for verification may report on the status of corrective measures, submit written evidence that relates to the quality of test results, and otherwise provide necessary explanations in document form within 30 days from the date on which parts that are non-compliant with the GLP for Chemical Substances are indicated to the notifier, etc. or applicant for verification. For the avoidance of doubt, the Office of Chemical Safety, Pharmaceutical Evaluation Division, Pharmaceutical and Food Safety Bureau will seek explanations directly from the relevant notifier, etc. or application for verification, when necessary, about the status of corrective measures, etc.

4) Evaluation

The GLP Evaluation Committee will eventually conduct evaluation according to the categorization of the status of compliance with the GLP for Chemical Substances in subparagraph 2) above based on results of the inspections, and materials and explanations of the notifier, etc. or applicant for verification in subparagraph 3), if available.

5) Responses on evaluation results to the Ministry of Health, Labour and Welfare

The GLP Evaluation Committee will give responses on results of evaluation of the status of compliance of the test facility with the GLP for Chemical Substances to the Ministry of Health, Labour and Welfare.

8 Measures Based on Evaluation Results of the GLP Evaluation Committee

1) Measures for study results

When the Director General of the Pharmaceutical and Food Safety Bureau judges “Fail” based on the evaluation results in paragraph 7-2), the study results generated based on the tests subject to the GLP for Chemical Results conducted at the relevant test facility subject to inspection will be excluded from the examination and other processes.

2) Notice of judgment results and notification of measures

(1) Notice of judgment results to the notifier, etc.

When the Director General of the Pharmaceutical and Food Safety Bureau judges “Pass” or “Fail” based on the evaluation results in paragraph 7-2), the Director General will notify

the notifier, etc. of judgment results in Form 3 or Form 4, both attached hereto, respectively. When the test facility is judged as "Fail," notice will be given that test results generated based on the tests governed by the GLP for Chemical Substances conducted at the relevant test facility subject to inspection cannot be adopted as inspection materials.

(2) Notice of Pass/Fail of verification to the applicant for verification

When the Director General of the Pharmaceutical and Food Safety Bureau judges "Pass" or "Fail" based on the evaluation results in paragraph 7-2), the Director General will notify the applicant for verification thereof in Form 5 or Form 6, both as attached hereto, respectively.

9 Handling of a Test Facility, etc. that Has Rejected the Inspection

When it becomes clear that the notifier, etc. or the test facility subject to inspection has rejected inspection under these Guidelines, or has given false explanations or responses in the inspection, the Ministry of Health, Labour and Welfare will take measures as if the relevant test facility and the tests subject to inspection had been judged as "Fail" set forth in paragraph 7-2).

10 Special Inspections

Notwithstanding the provision of paragraph 4 of these Guidelines, inspections shall be conducted under the following procedures, in either of the following 1) or 2):

1) When, after the judgment of results of the studies of new chemical substance or its hazardous properties, it becomes necessary to check the quality, etc. of the tests governed by the GLP for Chemical Substance to which the test results submitted in connection with the underlying notification.

(i) Procedures, measures, etc. of inspection will be determined, as appropriate, depending on details of the requirements for conducting inspections.

(ii) With respect to evaluation of inspection results, opinions of the GLP Evaluation Committee will be sought, when necessary.

2) When an inspection of the test facility governed by the GLP for Chemical Substances in Japan is requested by a foreign government body. However, this does not apply when the inspection was conducted under this request within the past three years from the date on which the request was made and the results of evaluation was "Pass" set forth in paragraph 7-2) of these Guidelines.

(i) paragraphs 5, 6 and 7 of these Guidelines will apply mutatis mutandis to the inspection procedures, reporting of inspection results, and evaluation of inspection results. In this case, the term "notifier, etc. or applicant for verification" is deemed to be replaced with "head of the test facility subject to inspection."

(ii) Forms Nos. 3 through 6 attached hereto are applicable to the notice of judgment results of inspections to the test facility, etc.

Form 1

PFSB Notification
●●●● No.●●
[Date]

To [Name of Notifier, etc.]

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

Notice of the Conduct of Inspections under the GLP for Chemical Substances

As it is necessary to conduct examinations or studies under the provisions of Article 4 (including the cases where it is applied mutatis mutandis pursuant to Article 7) of the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973; hereinafter referred to as the "Act"), Article 5 of the Act, Article 10, paragraph (1) of the Act, Article 10, paragraph (2) of the Act or Article 14, paragraph (1) of the Act, inspections will be conducted as follows:

Particulars:

1 Name of chemical substance subject to inspection

2 Test facility subject to inspection

3 Test items subject to inspection

4 Period of inspections (from [date] to [date])

5 Remarks
*(Date of notification) should be described, when necessary.

Form 2

PFSB Notification
●●●● No.●●
[Date]

To (Name of applicant for verification)

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

Notice of the Conduct of Inspections under the GLP for Chemical Substances

We will conduct inspections of the test facility identified below for which the application for verification was submitted dated [date] pursuant to the provisions of paragraph 3 of "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7, and EHD Notification No. 110331011, dated March 31, 2011), as follows:

Particulars:

1 Test facility subject to verification

2 Test items subject to verification

3 Period of inspections (from [date] to [date])

Form 3

PFSB Notification
●●●● No.●●
[Date]

To [Name of Notifier, etc.]

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

# Written Confirmation of GLP-Compliant Test Facility

As a result of the inspection conducted under the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7, and EHD Notification No. 110331011, dated March 31, 2011) to which the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973) pertains, we hereby confirm that the test facility and chemical substance test identified below are compliant with the "Principles for Test Facilities Conducting Tests of New Chemical Substances" set forth in "Principles for Test Facilities Conducting Tests of New Chemical Substances" (PFSB Notification 0331 No. 8 of PFSB, MIB Notification 23.03.29 No. 6, and EHD Notification No. 110331010, dated March 31, 2011).

Particulars:

1. Name of test facility
2. Location of test facility
3. Chemical substance subject to inspection
4. Test items
5. Effective period
   From [date] to [date]
6. Remarks

   *(Date of notification) and/or (date of inspection) should be described, when necessary.

Form 4

PFSB Notification
●●●● No.●●
[Date]

To [Name of Notifier, etc.]

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

# Written Notice of Non-Compliance

As a result of the inspection conducted under the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7, and EHD Notification No. 110331011, dated March 31, 2011) to which the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973) pertains, we hereby confirm that the test facility and chemical substance test identified below are non-compliant with the "Principles for Test Facilities Conducting Tests of New Chemical Substances" (Notification) set forth in "Principles for Test Facilities Conducting Tests of New Chemical Substances" (PFSB Notification 0331 No. 8, MIB Notification 23.03.29 No. 6, and EHD Notification No. 110331010, dated March 31, 2011).

Particulars:

1. Name of test facility
2. Location of test facility
3. Chemical substance subject to inspection
4. Test items
5. Remarks

*(Date of notification) and/or (date of inspection) should be described, when necessary.

Appendix

Items that are non-compliant with the GLP for Chemical Substances

1 Test facility subject to inspection

2 Tests subject to inspection

Form 5

PFSB Notification
●●●● No.●●
[Date]

To (Name of applicant for verification)

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

# Written Confirmation of GLP-Compliant Test Facility

As a result of the inspection conducted under the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7, and EHD Notification No. 110331011, dated March 31, 2011) to which the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973) pertains, we hereby verify that the test facility identified below is compliant with the "Principles for Test Facilities Conducting Tests of New Chemical Substances" set forth in "Principles for Test Facilities Conducting Tests of New Chemical Substances" (PFSB Notification 0331 No. 8, MIB Notification 23.03.29 No. 6, and EHD Notification No. 110331010, dated March 31, 2011).

Particulars:

1. Name of test facility
2. Location of test facility
3. Test items
4. Effective period
   From [date] to [date]
5. Remarks

   * (Date of application for verification) and/or (Date of inspection) should be described, when necessary.

Form 6

PFSB Notification
●●●● No.●●
[Date]

To (Name of applicant for verification)

Director-General, Pharmaceutical and Food
Safety Bureau, Ministry of Health, Labour and
Welfare

# Written Notice of Non-Compliance

As a result of the inspection conducted under the "Guidelines for Verification of Compliance with the Principles for Test Facilities" attached as an Appendix to "On the Handling of Test Results to be used as Judgment Data in Evaluation, etc. of New Chemical Substances" (PFSB Notification 0331 No. 9, MIB Notification 23.03.29 No. 7, and EHD Notification No. 110331011, dated March 31, 2011) to which the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973) pertains, we hereby confirm that the test facility identified below is non-compliant with the "Principles for Test Facilities Conducting Tests of New Chemical Substances" set forth in "Principles for Test Facilities Conducting Tests of New Chemical Substances" (PFSB Notification 0331 No. 8, MIB Notification 23.03.29 No. 6, and EHD Notification No. 110331010, dated March 31, 2011).

Particulars:

1. Name of test facility
2. Location of test facility
3. Test items
4. Remarks

* (Date of application for verification) and/or (Date of inspection) should be described, when necessary.

Appendix

Items that are non-compliant with the GLP for Chemical Substances

1. Test facility subject to verification

2. Tests subject to verification