General Questions and Answers Concerning OECD Principles of Good Laboratory Practice (GLP) and Mutual Acceptance of Data (MAD)

(6 November, 2015)

I. OECD Good Laboratory Practice (GLP)

1) What are the OECD Principles of Good Laboratory Practice (GLP)?

a) The Principles of Good Laboratory Practice (GLP) are a managerial quality control system covering the organisational process and the conditions under which non-clinical health and environmental studies are planned, performed, monitored, recorded and reported. The OECD Principles of GLP are followed by *test facilities* carrying out studies to be submitted to national authorities for the purposes of assessing the health and environmental safety of chemicals and chemical products which may also be of natural or biological origin and, in some circumstances, may be living organisms. Depending on the jurisdiction, the Principles of GLP can also be applied to non-clinical safety testing of other regulated products, such as medical devices.

b) The Principles of GLP define the responsibilities of test facility management, study personnel and quality assurance personnel that are operating within a GLP system, and minimum standards concerning the suitability of facilities and equipment to perform studies, the need for standard operating procedures, documentation of raw data, study reports, the archiving of records, etc.

2) What is a test facility?

A *test facility* includes the persons, premises (e.g. a testing laboratory) and operational unit(s) that are necessary for conducting a non-clinical health and environmental safety study (see below). For multisite studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities.

3) What types of tests are carried out at such facilities under GLP?

a) The OECD Principles of GLP concern "*non-clinical*" testing of a chemical or chemical product, examined under laboratory conditions or in the environment, including work conducted in greenhouses and in the field. They do not include studies which use human subjects.

b) Examples of studies carried out under GLP include, *inter alia*:

i) physical-chemical testing;

ii) toxicity studies;

iii) mutagenicity studies;

iv) environmental toxicity studies on aquatic and terrestrial organisms;

v) studies on behaviour in water, soil and air; bioaccumulation;

vi) studies to determine pesticide residues in food or animal feedstuffs;

vii) studies on effects on mesocosms and natural ecosystems; and

viii) analytical and clinical chemistry testing.

4) What types of chemicals / chemical products are covered under the OECD Principles of GLP?

a) The OECD Principles of GLP apply to the non-clinical safety testing of test items contained in:

i) pharmaceutical products;

ii) pesticide products (including biocides);

iii) cosmetic products;

iv) veterinary drugs;

v) food additives;

vi) feed additives; and

vii) industrial chemicals.

Depending on the jurisdiction, the Principles of GLP may also be applied to non-clinical safety testing of other regulated products, such as medical devices.

b) Under **GLP**, a *"test item"* is the article that is the subject of a study, and is frequently a synthetic chemical, but may be of natural or biological origin and, in some circumstances, may be living organisms. While the test item is the subject of a study, other testing *associated* with the test item and part of the test study (e.g., biological samples which are taken and analysed for the content of a test item and/or its metabolites) still need to be conducted under GLP.

(*Note*: The term "*test chemical*" has been applied in new and updated OECD Test Guidelines since 2013 to designate what is being tested. However, it is important to note that previously adopted OECD Test Guidelines still use the terms "test item", "test compound", "test substance" or other similar terms to describe what is being tested. The term "*test chemical*" is without prejudice on the applicability of the Test Guideline to individual chemical substance or mixtures; in case of restrictions, the Guideline will clarify what these are in the *Limitations* section.")

5) How do governments know that a study conducted at a test facility was carried out according to the OECD Principles of GLP?

OECD countries in which non-clinical health and environmental safety testing is carried out according to the OECD Principles of GLP have established national GLP Compliance Monitoring Programmes (CMP) with responsibilities for monitoring GLP compliance of test facilities within their territories (see *Guidance for GLP Monitoring Authorities; Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice*.) GLP compliance is verified by CMPs through inspections of GLP test facilities, and audits of GLP studies. A test facility which has been subject to periodic inspections by a CMP, and found to be operating in compliance with the Principles of GLP, is recognised as a GLP compliant facility.

6) How can test facilities become recognised as GLP-compliant?

Any test facility that conducts non-clinical health and safety studies (e.g., a university, research institute, private enterprise, government, etc.) can become OECD GLP-compliant or recognised. (This includes facilities in OECD member countries as well as non-OECD economies who become full adherents to the Mutual Acceptance of Data (MAD) system – *see* Section II below.) In most countries, facilities that wish to become recognised as GLP compliant can apply to the government CMP. The CMP then conducts an inspection to determine if the facility complies with the OECD Principles of GLP. In other countries, CMPs can inspect any test facility claiming to conduct studies according to GLP.

7) Why are the OECD Principles of GLP needed?

a) In the 1970's, prior to the introduction of GLP, some governments discovered fraudulent studies had been submitted by testing laboratories to regulatory authorities. As a result, OECD governments decided that there would be value in developing a set of *principles* – applied across all OECD countries – concerning the generation of quality test data. This would ensure that before making regulatory decisions concerning the safety of chemicals that will enter the market (or are already on the market), governments would have confidence that the data upon which they make their decisions is valid and of high quality.

b) Through standards built into the OECD Principles of GLP which allow the "traceability" of studies, CMP inspectors who visit test facilities can audit the results of a study long after it has been completed. This provides another level of confidence to regulators about the validity and integrity of data they are reviewing.

c) Further, as the application of GLP is harmonised across OECD countries, governments can accept data from other countries with the assurance that it will be valid and of high quality. (See discussion of the Mutual Acceptance of Data (MAD) system below.)

8) Are authorities actually inspecting test facilities?

Yes. Government CMPs conduct periodic inspections of test facilities within their country and perform random study audits.

9) Are the OECD Principles of GLP - established in 1997 - still relevant today given advances in testing methods?

Yes. The OECD Principles of GLP make up a general framework concerned with the *process* a test facility uses to conduct a test, not the specific substance being tested, nor the scientific approach followed when carrying out a test. Thus, the OECD Principles of GLP do cover all types of tests, including those not envisioned when the Principles were first established. However, OECD does periodically publish *advisory* documents which provide additional guidance or clarity concerning the application of GLP to new testing approaches (e.g., guidance for *in vitro* test methods).

II. OECD System of Mutual Acceptance of Data (MAD)

10) What is OECD's Mutual Acceptance of Data (MAD) system?

The OECD Mutual Acceptance of Data (MAD) system is a multilateral agreement which allows participating countries (including non-member economies) to share the results of various non-clinical tests done on chemicals. Under MAD, a non-clinical chemical safety study developed using *OECD Test Guidelines* and *OECD Principles of Good Laboratory Practice* (GLP) in one Member country or non-Member full adherent, **must** be accepted for assessment purposes in all member and adhering countries. This is the concept of "tested once, accepted for assessment everywhere."

11) What is the legal framework for the MAD system?

The multilateral agreement is composed of three OECD Council Acts (adopted by OECD ambassadors):

i) The 1981 Council Decision on the Mutual Acceptance of Data in the Assessment of Chemicals (revised in 1997) that states that test data generated in any member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice (GLP) shall be accepted in other member countries for assessment purposes and other uses relating to the protection of human health and the environment.

ii) The 1989 Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practices which establishes procedures for monitoring GLP compliance through government inspections and study audits as well as a framework for international liaison among monitoring and data-receiving authorities.

iii) The 1997 Council Decision on the Adherence of Non-Member countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals that sets out a step-wise procedure for non-OECD economies to take part as full members in this system.

12) Why was the MAD system established?

a) As many of the same chemicals are produced in more than one country (or are traded across countries), different national chemical control policies can lead to duplication in testing and government assessment, thereby wasting the resources of industry and governments alike. Furthermore, differences in regulations and test standards discourage research, innovation and growth and they increase the time it takes to introduce a new product onto the market. They can also lead to inefficiencies for governments, because authorities cannot take full advantage of the work of others which would help reduce the resources needed for chemicals control. It is for these reasons, that OECD has developed and is implementing the Mutual Acceptance of Data (MAD) system.

b) By reducing duplication, and creating a framework for the sharing of work, the MAD system saves governments and industry around €150,000,000 each year[1].

[1] *Cutting Costs in Chemicals Management* (OECD, 2010).

13) Is the primary aim of the MAD system to save money for industry?

No. The primary aim of the MAD system is to help governments protect human health and the environment. But, there are many other benefits: fewer duplicative tests means there is a reduction in both costs *and the number of laboratory animals* needed. In addition, as a result of the harmonisation of test methods and GLP, governments are able to collaborate on assessments of the same chemicals and "share the burden" of assessing the thousands of chemicals which are on the market. As a result, governments can assess chemicals faster and more cost effectively. For example, as a result of MAD, governments have been able to work together to assess chemicals through OECD's Hazard Assessment Programme, which uses data generated according to OECD Test Guidelines and GLP, [http://www.oecd.org/chemicalsafety/risk-assessment/oecdcooperativechemicalsassessmentprogramme.htm]. Under this Programme, more than a 1,000 high production volume chemicals were assessed, and countries have used these assessments for their national chemicals management activities (e.g. for classification and labeling).

14) How does one government participating in the MAD system have confidence in the quality and integrity of data generated in another country in the system?

a) To enhance mutual confidence in GLP Compliance Monitoring Programmes among participating OECD member countries and non-member economies, the OECD Working Group on GLP has established a programme of On-Site Evaluations of each country in the MAD system. Every national GLP Compliance Monitoring Programme is subject to a regular on-site evaluation visit, normally every ten years. The evaluation includes a review of the documentation of the GLP monitoring programme that is being examined, and an on-site evaluation visit to that programme to observe a full GLP inspection from start to finish, including associated study audits. A team of two or three representatives from other GLP Compliance Monitoring Programmes participate in the site visit.

b) The report of the on-site evaluation team, reviewed by the Working Group, has two primary aims: (i) to inform the members of the Working Group on GLP about the organisation, practices and procedures of the Monitoring Programme evaluated; and (ii) to describe the degree to which they are adhering to the 1989 Council Act.

15) How do non-member economies join the MAD system?

There is a step-wise procedure for non-OECD economies to become full adherents to MAD.

i) *First*, the non-member economy's government confirms that it will *provisionally* adhere to MAD. That is, it agrees to accept, for assessment purposes, non-clinical data generated in the testing of chemicals with OECD Test Guidelines and OECD Principles of Good Laboratory Practice from countries adhering to the OECD Council Acts on MAD. However, OECD countries and *full* adherents are not obligated to accept data for assessment purposes from the provisional adherent. This is because the provisional adherent's GLP Compliance Monitoring Programme (CMP) has not yet been evaluated by OECD.

ii) *Second*, as the provisional adherent is setting up a GLP CMP, it is invited to attend OECD Working Group on GLP meetings and training courses, and to serve as an observer in on-site evaluations of other countries.

iii) *Third*, once the provisional adherent has fully developed its GLP CMP according to OECD guidance, an On-Site Evaluation visit is carried out. Based on the outcome of this visit, if the OECD concludes that the provisional adherent's GLP Compliance Monitoring Programme is in accord with the OECD Council Acts on MAD, the country becomes a "*full*" adherent to MAD. As a full adherent, all non-clinical study data conducted in that country according OECD Test Guidelines and OECD Principles of Good Laboratory Practice **must** be accepted for assessment purposes in all 34 OECD member countries and adhering non-member economies.

16) What is a full adherent to MAD?

A full adherent is a non-member economy whose GLP Compliance Monitoring Programme has been evaluated by OECD and complies with the OECD Council Acts on MAD (see question 11). As a result, non-clinical health and environmental safety testing of chemicals and chemical products conducted in a full adherent in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice, shall be accepted for assessment purposes in OECD Member countries, provisional adherents and other full adherents.

17) Which non-OECD countries are full adherents to MAD?

As of November, 2015, ***Argentina, Brazil, India, Malaysia, Singapore*** **and** ***South Africa*** are full adherents. (More information on full and provisional adherents can be found here.)

18) What is meant by "acceptance" of data generated within the MAD system?

a) Once a country receives study data for assessment purposes from a MAD adherent country it cannot ask that the study be repeated. That is the concept of "test once, accepted for assessment purposes everywhere". However, how the receiving country *interprets* study results is its own prerogative.

b) Further, if a country does not require or need data on a particular hazard endpoint (e.g., acute inhalation toxicity) to conduct its chemical assessments, but it receives a MAD compliant study on that endpoint, it is up to that government to decide how, if at all, it uses the study in its assessment.

19) Is a government restricted to using only MAD compliant studies when assessing the safety of a chemical for regulatory purposes?

No. All governments should ensure they have the best scientific evidence concerning the safety of a chemical before drawing any conclusions about the chemical. They are free to set their own quality requirements for non-clinical data and to accept the results of a study that was not conducted according to an OECD Test Guideline and according to OECD GLP if they believe it is scientifically valid. While the MAD system promotes the sharing of quality (and verifiable) data on test results, governments can always require more tests if they need additional information upon which to base a decision or if there are confounding results. Finally, governments also use a weight-of-evidence approach when assessing the safety of a chemical, and, thus, may take into consideration older studies that were conducted before an OECD Test Guideline for that endpoint was developed or studies that are based on novel methods for which a Test Guideline has yet to be developed.

20) If a provisional adherent only has a Compliance Monitoring Programme for one product type (e.g., industrial chemicals), must it accept data on all product types from other MAD countries?

Yes, with the exception stated in 18b).

21) If a full adherent or OECD country only has a Compliance Monitoring Programme for one product type (e.g., industrial chemicals), must OECD members and adherents to MAD accept data on other product types tested in the full adherent (e.g., pesticides)?

No. Countries that are part of the MAD system are only required to accept test data on a particular product type from another country in the system, if that country has a Compliance Monitoring Programme for the product type being tested.

22) Must governments who are part of the MAD system accept <u>products</u> that have been tested according to the OECD Principles of GLP?

No. MAD only applies to non-clinical health and safety *studies*. Each government can reach its own conclusion as to the risk posed by a chemical based on those studies, and, from that, make a decision as to whether the product that was tested can be placed on (or imported into) the market.

23) If a test facility is in a country that is <u>not</u> an adherent to MAD, but has been inspected by a country that <u>is</u> an adherent, must other MAD countries accept data from this facility?

No. Countries which adhere to MAD are only required to accept GLP data that has been generated in other countries that are full adherents.