DRAFT OECD GLP ADVISORY DOCUMENT NO. 19 ON THE MANAGEMENT, CHARACTERISATION AND USE OF TEST ITEMS

PREAMBLE

1. This guidance provides clarity for test facilities on the expectations of national Good Laboratory Practice (GLP) compliance monitoring authorities on how test items are received, characterised, sampled, handled, stored, archived and destroyed. The document consolidates existing OECD guidance on test items that are used in studies conducted in accordance with the Principles of GLP. It also aims to promote a consistent approach that is appropriate to the objective of the study and the nature of the test item.

1. SCOPE

2. This document is designed to provide guidance on:

- the transportation, identity, receipt, handling, storage, archiving and disposal of all test items used on GLP studies; and
- the expectations on the characterisation of different types of test items that are used in the conduct of a broad range of non-clinical safety studies carried out in accordance with GLP. Test items include agrochemicals, industrial chemicals, pharmaceuticals and biological agents (vaccine, antibody, enzyme, etc.). The scope of the guidance also covers formulated test items and medical devices.

3. The scope of this document does not include reference items.

2. DEFINITIONS OF TERMS

2.1. Test Item

4. Test item is defined as an article that is the subject of a study. This includes synthetic and naturally occurring chemicals, biological agents, live organisms and medical devices. It should be noted that test item is also referred to as "test chemical" in some of the OECD Test Guidelines[1].

[1] *Terminology in OECD Test Guidelines to designate what is tested. In June 2013, OECD's Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology agreed that where possible with respect to Test Guidelines, a more consistent use of the term "test chemical" describing what is being tested should now be applied in new and updated Test Guidelines. However, it is important to note that previously adopted OECD Test Guidelines will still use the terms "test item", "test compound", "test substance" or other similar term to describe what is being tested." The intention of this proposal is not to provide a new definition of the term "chemical(s)", but rather to be consistent with the UN definition of it when applicable, i.e. in Test Guidelines that make reference to the UN GHS for Classification and Labelling where "chemical" means "substance and mixture".*

2.2. Batch

5. Batch is defined as a specific quantity or lot of a test item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.

2.3. Vehicle

6. Vehicle is defined as any agent that serves as a carrier and is used to mix, disperse, or solubilize the test item to facilitate the administration/application to the test system.

2.4. Formulation

7. Formulation is the combination of a test item and vehicle obtained by mixing, dispersion and/or solubilisation which is administered to the test system. A test item which is capsulated or packed in some other way for the purposes of delivery is not regarded as a formulation in this document.

2.5. Characterisation

8. Characterisation is attributes of the test item which collectively provide evidence that it is suitable to fulfil the objectives of a GLP study.

2.6. Identification

9. Identification of the test item means the process of assessing and checking information including labelling, prior to undertaking a GLP study.

2.7. Test system

10. Test system means any biological, chemical or physical system or a combination thereof used in a study.

2.8. Expiry Date (or Expiration Date)

11. Expiry Date (or Expiration Date) is the designated time during which a test item is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

2.9. Retest Date

12. Retest Date is the date a test item should be re-examined to ensure that it is still suitable for use.

3. RESPONSIBILITIES

3.1. Test Facility Management

13. Test Facility Management should ensure that test items are appropriately characterised and that there are written procedures which describe how test items are received, identified, labelled, handled, stored, sampled and archived. These procedures should describe the actions and responsibilities required to ensure that the test item is suitable to fulfil the objectives of a GLP study.

3.2. Study Director

14. The Study Director has overall responsibility for the GLP compliance of the study. Therefore, the study director needs to fully understand and have confidence in the test facility procedures used to characterise the test item and to assure him or herself that the test item is what it purports to be, prior to undertaking the study.

3.3. Quality Assurance personnel

15. The Quality Assurance personnel undertake the activities of the Quality Assurance Programme. The Quality Assurance Programme should include inspections to verify the implementation of relevant procedures and practices, such as identity, receipt, characterisation, labelling, handling, sampling and storage of test items.

4. TEST ITEM TRANSPORTATION AND RECEPTION

16. An assessment of the integrity of the test item and verification of its identity upon reception is important to confirm that it is suitable for use in the study(ies). The assessment should take into account the conditions the test item was exposed to during transportation and the physical condition of the test item and its container upon arrival.

17. Prior to sending the test item there should be a mechanism, developed in co-operation between the sponsor (or the sender) and the test facility, to establish the conditions the test item is expected to be subject to during transportation. In order to preserve the integrity of the test item, care should be taken to avoid test items being exposed to detrimental environmental conditions, especially if they are temperature, light and/or humidity sensitive. Appropriate monitoring measures, such as the use of data loggers, max/min thermometers or the visual check of the presence of dry ice on arrival should also be put in place.

18. Environmental conditions during transportation, where monitored, and the condition of the test item and its container upon arrival at the facility should be recorded and these records should be retained.

19. For each GLP study there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item. The identity of the test item should be assessed upon arrival at the test facility. The assessment should include verification that the information on the container the test item is shipped in and the labelling on the test item, matches the information recorded on the certificate of analysis or other relevant documentation. These checks may include a comparison with information the sponsor has provided prior to receipt.

20. Checking that the physical characteristics of the test item, such as colour and consistency, match the physical characteristics detailed on the certificate of analysis or other associated documentation is an important part of the verification process. The extent and depth of what is physically checked can vary from test item to test item and should be justified. Evidence of these checks should be documented and retained.

21. When relevant, the original container and labelling on the test item (or picture of it) may be retained in order to verify the identity of the test item.

22. Once the test item has been received by the test facility, chain of custody records should be maintained and retained.

5. HANDLING AND STORAGE

23. Some test items require special handling and storage conditions because of their physical/chemical/biological properties; for example, test items may be light sensitive, hygroscopic, require refrigeration or freezing. In such cases, the chain of custody records should positively document the time and date the test item was received by the facility and when it was transferred to an appropriate storage location in order to maintain its integrity prior to use.

24. Records of the quantity of test item received, the amount used during the conduct of the study, and the quantity remaining at the end of the study should be maintained. Responsibilities for the maintenance of records should be defined by the test facility management.

25. Storage container(s) should carry unique identification information such as name, batch number, expiry date, and specific storage instructions. If a test item is stored in containers which are small or difficult to label, it would be appropriate to assign a unique reference number or identifier to the container which is traceable to more comprehensive information either in paper or electronic format.

26. To prevent cross contamination or potential confusion between test items, there should be separate rooms or areas for the receipt, storage and mixing of test items with a vehicle. Methods used to prevent cross contamination, such as separation in terms of location and/or time, cleaning or decontamination should be described in procedures.

27. Storage rooms or areas for the test items should be separate from rooms or areas housing the test systems. Storage facilities should be adequate to ensure the test item remains suitable for use on the study(ies).

6. CHARACTERISATION OF THE TEST ITEM

6.1. General information

28. The GLP Principles require information on identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test item. Therefore, it is expected that a GLP study is only initiated when information is available on the characterisation and identity of a test item to confirm it is what it purports to be.

29. Verification of the identity of the test item is an integral part of ensuring the integrity of a GLP study and consequently great importance should be placed on the system used to confirm that the test item is suitable for use in the study.

30. The extent to which a test item will be characterised may be commensurate with the stage of product development. In the earlier stages of test item development there may be less characterisation information available. Nevertheless, the minimum amount of characterisation information required by the Principles should be available before completion of a GLP study or the lack of such information should be outlined in the final report.

31. No or inadequate information on the characterisation of the test item constitutes a deviation from the Principles of GLP and should be documented accordingly. The impact this deviation has on the validity of the study data and the extent of compliance with GLP should be described in the study director’s statement.

32. Where multiple batches of test item are used during a GLP study, adequate characterisation information should be available for each batch of the test items used.

6.2. Identification

33. The GLP Principles require that for each study, the identity, including batch number, purity, composition, concentration, storage conditions or other characteristics to appropriately define each batch of the test item should be known. Mechanisms should be in place within the test facility to verify the identity and properties of test items. Test items may be supplied with a certificate of analysis, which usually provides basic information on the physical characteristics of the test item, the batch number and the expiry date. In the absence of a certificate of analysis, an alternative mechanism should be implemented to verify the identity of the test item. For example, sufficient information to confirm the identity and properties of the test item may be supplied in alternative formats such as a laboratory report, memo or a letter from the sponsor. Information supplied about the identification of a test item should be retained.

6.3 Expiry date

34. The supplier of the test item should provide the test facility with information on the expiry and/or retest date. A distinction should be made between expiry dates, which should be based on actual stability data, and retest dates, which could be an arbitrary period of time assigned before it is deemed necessary to retest the test item to ensure it has not degraded. If a retest date is provided rather than an expiry date, the test facility management should be aware of the relevance of it. The final report should document if a retest date or an expiry date is available.

35. New retest dates or an expiry date should be accepted only if there is sound scientific rational to support the new date, and this data should be retained.

6.4. Characterisation data

36. The characterisation of the test item may be carried out by the sponsor, a supplier or the test facility. If characterisation is performed by the sponsor or a supplier, test facility management should ensure that documented procedures describe the extent and depth of checks that should be performed to assure the integrity and quality of information supplied by the sponsor or supplier.

37. In every case, the responsibility of the characterisation and the quality standard that characterisation was performed under should be described in the final report.

6.5. Characterisation for specific test items

6.5.1. Biochemical

38. If the test item is a biochemical, for example an antibody, a peptide, viral vector or an enzyme, the need for information to verify biological activity should always be considered including the determination method and its quantification (potency) as part of the characterisation process. If no information is provided to demonstrate the biological activity of the test item, the reasons why the test item is still considered suitable for use in the study should be clearly outlined in the final report.

6.5.2. Living Organisms

39. If the test item is a living organism, for example a cell line, a virus or a microorganism, the characterisation may require specific information on properties which are unique to the test item. For example, if the test item is a cell line, it may be appropriate to confirm passage number. If the organ-

isms are derived from a culture collection, such collections typically maintain detailed records of suppliers of cultures showing the material sent (with strain and batch numbers where appropriate), method and date of shipment, and name and address of the person who sent it Other biological properties that may be taken into consideration because they have an impact on the viability of the test item may include proliferation rate, culture conditions or infectious titer determination. In all cases, the information required to characterise living organisms such as the identity should be considered on a case by case basis and the rational for performing the tests described in the study plan.

6.5.3. Transgenic organisms

40. In certain situations, a test item may be a transgenic organism[2]. A lot of transgenic organisms used in GLP studies are of plant/crop species. If an OECD unique identifier is available (ENV/JM/MONO(2002)7), this can be included. If information is available on seed certification, this can also be used. Alternatively, the name of the host species, a description of the inserted genetic material and the trait should also be given, along with the name of the developer of the transgenic organism.

6.5.4. Medical devices

41. For studies on medical devices, characterisation data can include the description of the device, the lot number, the types of materials the device is made of (and method of manufacture and name of the manufacturer of any polymers, colorants, metals), the methods of manufacture and synthesis of the final device (e.g. injection molding) and the location of manufacturing facilities.

42. An illustration or a photo could be the best way to show the entire configuration of the medical device.

43. For medical devices, the date of manufacture, stability, and storage conditions should be known and documented. Where applicable, information on the sterilisation status of the device used as a test item should be provided by the supplier.

44. If the test item is only a part of a medical device, the characterisation of the full medical device should be available.

6.5.5. UVCBs

45. Substances of unknown or variable composition (UVCBs), complex reaction products or biological materials cannot be sufficiently identified by their chemical composition because the number of constituents is relatively large and/or the composition is, to a significant part, unknown and/or the variability of composition is relatively large or poorly predictable. In such cases, the composition could then be defined by the manufacturing process description.

6.5.6. Separation steps

46. When separation steps are carried out during the preparation of the test item, for example centrifugation, decantation, filtration and chromatograph, etc., those steps should be documented and the impact of such steps on the preservation of the characteristics of the test item should be assessed and documented.

[2] There are different terms for transgenic organisms in different countries. Commonly used terms include: genetically modified organism (GMO), genetically engineered organism (GEO) and living modified organism (LMO). There are other variations on this theme.

7. TEST ITEM ADMINISTERED OR APPLIED IN A VEHICLE

7.1. Formulation Preparations

47. The responsibility of the formulation preparation and the quality standard that formulation preparation was performed under should be described in the final report. This requirement is particularly significant in cases of supplied ready-to-use test item formulations.

48. Dosing preparation for medical devices could be either the intact medical device, extract from the device using adequate solvent and conditions, or mixture with a vehicle.

7.2. Data on homogeneity, concentration and stability of the formulations

49. If the test item is administered or applied in a vehicle, homogeneity, concentration and stability of the test item in that vehicle should be determined and reported. There is an expectation that data on homogeneity, concentration and stability of the formulations are generated in accordance with the Principles of GLP.

50. There is no requirement for formulation analysis to be performed as part of the main GLP study; in some instances it may be more appropriate to perform the work as a standalone study, especially where the same formulation will be used for multiple GLP studies.

51. If the test item is supplied pre formulated in a vehicle and the formulation analysis data is generated in a non-GLP compliant facility, including GMP and that of the sponsor, the impact on the validity of the study and the integrity of the test item should be assessed and reflected in the final report.

52. For extracts from medical devices, data on the concentration may not be relevant. However, the stability and homogeneity of the extract might be relevant and it may be necessary to determine these before administration. In case of repetition of the extraction step, there may be a mechanism to confirm the extracts from the different extractions are equivalent (for example, description of aspect, monitoring of pH, osmolality, etc.).

53. It is recognised that it is not always technically possible to generate information on homogeneity, concentration and stability for test item formulations. The lack of such data and its impact on the validity of a study should be justified in the study report.

8. ARCHIVING

54. The OECD Principles of GLP require that a sample from each batch of test item should be retained and archived for analytical purposes for all studies except short-term studies. To allow the sample to be the most representative of the supplied test item, the retained and archived sample may be preferentially sampled immediately after reception or at the first opening of the container then stored in the appropriate conditions.

55. The OECD Principles of GLP require that a test item needs to be archived for as long as its quality permits evaluation.

56. The retention period should be defined based on an assessment taking into account the stability of the test item, the recommended retention time, and also safety and regulation requirements (e.g. hazardous or regulated test item).

9. DISPOSAL

57. Disposal of the test item should be documented and performed according to established procedures and should comply with national requirements for the disposal of chemicals and biological products.