POSSIBLE POINTS TO CONSIDER FOR ALL-ANIMAL TEST SYSTEMS

- Justification for use: Many non-animal testing options are available. Evaluate the use of each test method.
- Consistent performance: Concurrent positive and negative assay controls can be used to verify proper test system performance in each assay. Monitoring test system performance during each use is not an ethical concern. The number of animal use may be minimized or eliminated under the revised test system.
- Point of becoming the GLP test system: Whereas in the typical animal testing paradigm, animals are received ready for testing (save the quarantine and veterinary oversight, identification and randomization), many, if not all, non-animal test methods require various steps to transform cells, new materials, reagents and test platformic into a defined GLP test System used in subsequent test protocols. Thus it is critical that we clearly identify criteria for when these new assays and reagents can be declared the test System. Quality procedures should be used in these manipulations and compliant documentation should keep GLP test system requirements met once the in vitro system has been prepared and is presented in the final platform used for dose exposure.

ABSTRACT

The use of non-human animal test methods transforms any regulatory requirements are applied in prescriptive testing. Recent global regulatory initiatives emphasize the importance of transitioning to human relevant assays and test systems that do not use animals. When these methods are moved from research into the regulated arena, GLP principles must be followed. The GLPs were originally written in the 1970s, when the vast majority of regulated research was performed using animals as the test system. Current innovative, alternative test systems include ex vivi tissues, manufactured biological systems, three dimensional tissue constructs, and cell subsets. This class of alternative test system raises new quality and compliance points to consider when used within a regulatory context. Just as the applications of these methods have advanced with regulatory acceptance, the quality control and compliance of these test systems must also progress.

INTRODUCTION

The Organization for Economic Cooperation and Development (OECD) defines a test system as “…any biological, chemical or physical system or a combination thereof used in a study,” in the Principles of Good Laboratory Practice as revised in 1997. OECD, 1997). The US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) both define a test system as “…any animal, plant, microorganism, or supports thereof to which the test or control animal is administered or added for a study,” (FDA 21 CFR 58; and EPA 40 CFR 161). The US EPA and FDA further include “…appropriate groups or components of the system not treated with the test or control animal,” as part of the test system. Good Laboratory Practices were established at a time when regulated safety and efficacy studies were almost exclusively performed on animal test systems. The US FDA and EPA, as well as the OECD GLPs reflected this status quo. In the early 1990s the US EPA revised their GLPs to reflect the broader scope of work covered by their regulations. While the FDA was largely focused on health testing, where animals were the majority of the test systems used, the scope of the EPA FIFRA GLPs included the use of plants and soil samples as test systems and the regulations were reviewed accordingly. Since that time, many assays that do not include whole animals have completed validation evaluation and have received OECD Test Guidelines. The table below provides a list of validated toxicological test methods that have received OECD Test Guidelines where animals, plants, and soil samples are not used as the test system.

CELL CULTURE

- Preparation of Test System
  - Source: Purchase cells from a reliable source and assure there is documentation on the identification of the cell line to protect against inadvertent use of incorrect cell types or strains, e.g. HEK.
  - Origin of the test material: vehicles and provide data on the consistency of the test system and reliability of the derived data over time.
- Cell Line Handling Documentation
  - Although not part of a specific study, records should be kept documenting the handling and treatment of the cell culture prior to preparation in the final platform for use in the assay:
    - chronology of custody
    - passage number
    - culture conditions and sub cultivation intervals
    - freezing/thawing conditions
    - Tracks personnel, media lots and expiry, confidentiality on all supplies and other culture manipulations in house prior to use in the assay.

EX VIVO

- Preparation of Test System: Particularly with ex vivo test systems, a great deal of processing and preparation is performed prior to identifying the test system and confirming its suitability for use in an assay. The entirety of the ex vivo entity is often not what is dosed in a test method, i.e. not the test system. Care should be taken to lock the preparation of the test system, but the GLP definition of the test system is not met prior to 1) meeting predefined acceptance criteria and 2) integration with the dosing platform.
- Identification of test system: OECD GLPs 5.2.3 require “records of source, date of arrival, and animal condition of test animals.” Ex vivo test systems derived from tissue biopsy (or biopsy from animals) will likely not have additional information available that is typical for whole animal test systems, such as age and sex. Although the animal is its own control, data collection is not possible or usually acceptable in ex vivo tissue. In many OECD guidelines, it is not as critical a measurement of test system suitability as protocol defined pre-dosing test system suitability measurements. For human based ex vivo test systems, specific data are often protected by national regulations protecting personal privacy.

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Cell Culture

- "Fluorescence Leakage Test Method for Identifying Ocular Corneal and Severe Irritants (OIC)" (HEOD 03) cell culture
- "Short Time Exposures in In Vivo Test Method for Identifying (Chemicals Inducing Serious Eye Damage and/or Chemicals Not Requiring Classification or Identification or Serious Eye Damage)" (OECD 411) Xenopus laevis-derived Cell Culture (XPECS) cell culture
- "In Vivo ST3 Neural Retinal Electrode Photostimulation Test" (BabiC37 Cells)
- "In Vivo Sensitization Test Method: Acute 96-Hour Sensitization (OECD 407)" K562 Cells
- "In Vivo Sensitization Test Method (Reconstructed Human Epithelial Cells)" (THP-1 Cells)

Manufactured Human Tissue Models

- "Reconstructed Human Cornea-Human Epithelial (BCE) Test Method for Monitoring Chemicals Not Requiring Classification and Labeling for Eye Irritation or Corneal Damage or Eye Damage" (OECD 412) 3-dimensional RHEC Tissue Constructs
- "Reconstructed Cornea Human Model Test" (OECD 413) 3-dimensional RHEC Tissue Constructs
- "In Vivo Skin Initiations/Reconstructed Human Epithelial Test Method" (OECD 414) 3 dimensional Reconstructed Human Epithelium (RHE) Constructs

REFERENCES

- The Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (ENV/AC/303)
- U.S. Food and Drug Administration Good Laboratory Practice for Non-clinical Studies, 21 CFRs Part58
- Environmental Protection Agency Good Laboratory Practice 40 CFR – Part 160, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
- U.S. Environmental Protection Agency Good Laboratory Practice Standards; Final Rule 40 CFR Part 792, Toxic Substance Control Act (TSCA)