Incorporating GIVIMP Recommendations into Method Development, Use, and Transfer

A. Ulrey, M. Gaydash

Institute for In Vitro Sciences, Inc. Gaithersburg, MD

ABSTRACT

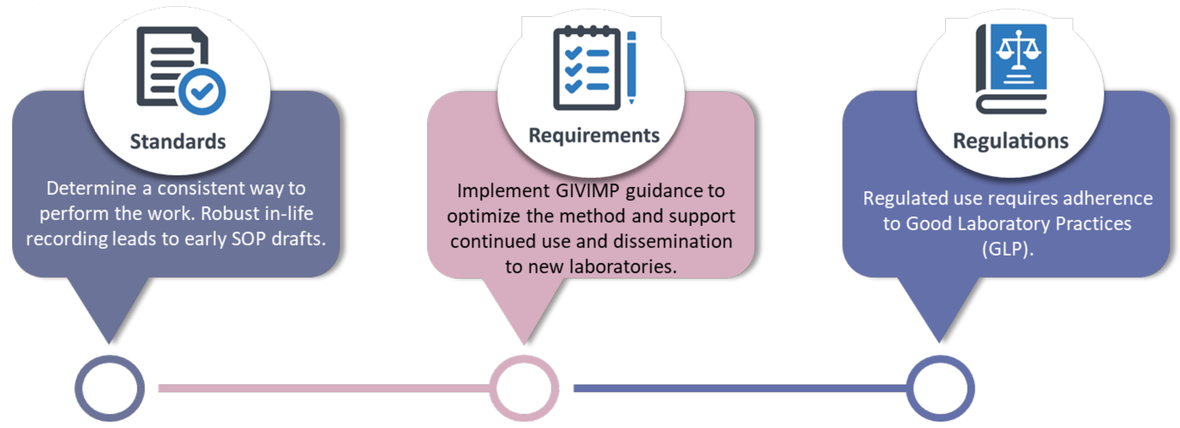
The demand for toxicology data from human-relevant, New Approach Methodologies (NAMs) continues to increase. Fortunately, the scientific community has responded with new tools based on human tissues and cells. The creators of these systems and test methods utilizing them have invested in their development and also in studies designed to demonstrate their relevance, reproducibility, and transferability. Despite these efforts, scientific confidence in these methods at the regulatory level remains comparatively low. In order to bridge the gap between development and acceptance, industry best quality practices need to be embraced by all stakeholders as early as possible in development and continue throughout the life cycle of a test method. The Good In Vitro Method Practices guidance document was published by the OECD in 2018 with an aim to "improve the reliability and robustness of *in vitro* methods, reducing the uncertainties of *in vitro* based predictions and therefore increasing the acceptance of the *in vitro* estimated safety measures by regulatory agencies" (OECD, 2018). The magnitude of the information presented in GIVIMP has led to challenges in its uptake and use by the *in vitro* testing community. This presentation provides points to consider for method developers and users, and test system providers implementing GIVIMP guidance within their laboratories as one step to improving scientific confidence in NAMs. Incorporating GIVIMP standards into standard laboratory procedures will improve the transparency and reproducibility of the methods developed and performed there, and increase the confidence of validation bodies, receiving authorities, and industry in NAMs.

What is GIVIMP?

The Good In Vitro Method Practices (GIVIMP) guidance aims to reduce the uncertainties surrounding *in vitro* method derived predictions. It was written jointly by the OECD Working Group on Good Laboratory Practices and the Working Group of the National Coordinators to the Test Guideline Program and coordinated by the European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) of the European Commission's Joint Research Centre (JRC). It is a document comprised of best practices and points to consider in the design and execution of laboratory work using cells and tissues as the test system (OECD, 2018).

GIVIMP addresses the topics shown in the circles below. Many of the recommendations center around the test system itself. Other points raised focus on controls for the equipment used, documentation and standardization of processes, training of personnel, and data integrity and record retention. Following the GIVIMP guidance leads to reliable results, technologies that are more easily transferred from the laboratory of origin to others, and robust records and documentation supporting the science.

Begin with the end in mind.
- Stephen Covey



Method Development
Begin utilizing GIVIMP to support data integrity and build evidence needed to document fit for purpose and establish scientific confidence in the method.

Routine Use and Transfer
Fully implement GIVIMP recommendations to support data integrity and maintain the credibility of the method and data derived from it over time.

Regulatory Use
Following GIVIMP for methods early smooths the transition to following Good Laboratory Practices (GLPs) for regulated work and data submissions later.

References

Coecke, S. et al (2019), "How the Good In Vitro Method Practices Guidance Document Can Help Implement New Toxicological Approaches: A Case Study in China". Poster presented at the Society of Toxicology Annual Meeting, March 10-14, 2019; Baltimore Maryland

Liu, Y. et al. (2023) "How to facilitate the implementation of 3D models in China by applying good in vitro method practice for regulatory use", Frontiers in Toxicology – Section In Vitro Toxicology, (5). https://doi.org/10.3389/ftox.2023.1080528

OECD (2018),"Guidance Document on Good In Vitro Method Practices (GIVIMP)" OECD Series on Testing and Assessment, No. 286, OECD Publishing, Paris, https://doi.org/10.1787/9789264304796-en

Ulrey, A., Kolle, S., Landsiedel, R. and Hill, E. (2021) "How a GIVIMP certification program can increase confidence in in vitro methods", *ALTEX - Alternatives to animal experimentation*, 38(2), pp. 316–318. http://doi: 10.14573/altex.2102261

van der Zalm, A.J., Barroso, J., Browne, P. *et al. (2022)* A framework for establishing scientific confidence in new approach methodologies. *Arch Toxicol* **96**, 2865–2879. https://doi.org/10.1007/s00204-022-03365-4

Points to Consider from GIVIMP for Test System Providers, Method Development, and Routine Use

The OECD guidance document titled Good In Vitro Method Practices (GIVIMP) is divided into 10 chapters. These chapters are represented in the circles below with a summary of their content. Some key points to consider are extracted from the chapters and presented in the table. They are organized into three categories: 1) Test System Provider, 2) Method Development, and 3) Routine Use. Manufacturers or providers of test systems should review the items noted under the Test System Providers column as they are the appropriate party to provide the information noted here. The recommendations under the Method Development header are those items it would be beneficial to address while still in the development and early optimization phase of the method. Points raised in the Routine Use column can be addressed once the method is standardized and is performed often within a laboratory or has been transferred to a new laboratory.

	Test System Providers	Method Development	Routine Use
1. Roles and Responsibilities ➢ Targets method developers, test system providers, validation bodies, inter-governmental organisations, suppliers, users and sponsors.	• Provide test system users with adequate information to properly operate and use the system • Document that test system characterization • Provide documentation of sterility	• Clearly written method description • Consider IP guidelines and follow good licensing practices	• Document competency to perform the work (e.g. proficiency chemicals) • Follow GIVIMP recommendations to maintain data integrity or GLPs for regulatory studies
2. Quality Considerations ➢ Examines quality risk-based assessment and quality control requirements for development and implementation of *in vitro* methods	• Provide users with information on acceptable performance limits of the test system • Document batch/lot acceptability • Train users where special training is warranted	• Begin gathering data to determine acceptance criteria for the method (control charts) • Perform quality risk assessment • Specify appropriate time intervals, temperature ranges, etc.	• Use control charts • Formal training on method procedures for staff
3. Facilities ➢ Recommends fit for purpose facilities and a detailed understanding of the work flow.	• Define laboratory requirements for use of the test system (BSL level, power) • Describe acceptable disinfectant and cleaning procedures to users	• Minimize the risk of mix-ups and cross-contamination • Understand the risk and mitigation needs for biological and chemical agents	• Quarantine procedures for new test systems • Dedicated areas for data storage and archival • Separate bacteria and yeast from cell and tissue culture work
4. Apparatus, materials and reagents ➢ Highlights the importance of regular maintenance, calibration, and validation ➢ Instructs on sourcing of materials and reagents (e.g. from well-established suppliers) to ensure the integrity and reliability	• Defined quality checks for the test system and consumable components • Are there recommended or required media and reagents for use with the test system	• Calibration of equipment prior to use • Record performance of equipment • Media details known and defined	• Appropriate labeling and storage of reagents • Is cell/tissue grade water used for routine cell culture work • Regular performance checks for pipettes
5. Test Systems ➢ Advises the setting of acceptance criteria already at the method development stage ➢ Describes identification and characterization, sourcing, cell-banking and cryopreservation	• Characterization of test system • Documentation of absence of contamination with each batch/lot • Proof that biological materials were obtained ethically	• Cells and tissues from a certified provider • Establish go/no go points • SOPs for test system handling	• Ensure both short and long term availability of the test system • Quarantine of new cells lines • Procedures for mycoplasma testing
6. Test and reference/control items ➢ Recommends to identify potential sources of interference with the test system and/or method endpoint	• Is reference data published so that it can be referenced by all users? • Are there classes of materials that will have unintended effects on the test system?	• Use control items to assess performance of the test system in the method • Selection of positive control • Identify the highest acceptable concentration of test item and solvents used	• Concurrent positive controls • Aseptic handling of test and reference items • Test an adequate number of concentrations of the test system
7. Standard operating procedures ➢ Describes the evolution of a SOP from initial method description to method optimization and validation.	• Standardize and document methods for test system production and use • Procedures for documenting deviations • Were methods standardized prior to the performance of validation activities	• Records describing the procedure in detail • Start a data set to track historical values for reference items and controls • Performance of in-house validation	• SOPs in place to support the main activities of the laboratory • Procedures for adapting SOPs to changes in processes • Personnel review revisions to SOPs
8. Performance of the method ➢ Analyses development of acceptance criteria for components (e.g. positive and negative controls)	Not Applicable	• Explanation of applicability domain, limitations, and exceptions • Determine clear cut off values and the mean and SD for the acceptance criteria • Documented procedures for transformation of data and data analysis	• Obtain acceptable results for the proficiency chemicals, where they are defined. • Use calibrated equipment for each run • Data to support successful transfer of the method to the laboratory
9. Reporting of results ➢ Recommends publishing of scientific data to promote more transparency and openness ➢ Reporting of method validation is also discussed	• Where there are IPR elements of the test system, provide generic descriptions of those components • Communicate performance standards, use instructions, and historical reference and control item ranges to users	• Determine and report within-laboratory repeatability and reproducibility • Report the predictive capacity • Use appropriate controls on data templates	• Put quality control procedures in place around the data to ensure that the reported data accurately reflects the work performed
10. Storage and retention of records and materials ➢ Discusses requirements relating to the storage and retention of data, records and materials	• Retain documents related to the development of the test system • Follow general principles of data integrity	• Retain raw data in lasting media (i.e. export data from the individual data capture machines) • Retain metadata along with the associated raw data • Follow general principles of data integrity	• Safeguard the quality of historical data • Retain ALL data in the archives • Follow general principles of data integrity