Improving Quality and Reliability of Data through Implementing Good In Vitro Method Practices (GIVIMP)

A. Ulrey and E. Hill

Institute for In Vitro Sciences, Inc., Gaithersburg, MD, USA

ABSTRACT

Over the past several years science has put renewed energy into improving the reproducibility of data. There are many articles, strategies, and tools to help with this that are specific to the field of *in vitro* toxicology, such as systematic reviews of published work (and tools to help educate on how to perform them), publishing Good Cell Culture Practices (and GCCP 2.0), improvements made to the method validation process itself, and increased acceptance and use of *in vitro* methods within the Good Laboratory Practices (GLP) quality system. Another tool for improving the reproducibility of *in vitro* work is the implementation of the practices described in the OECD's guidance document Good In Vitro Method Practices, or GIVIMP. The GIVIMP guideline is applicable to academic laboratories developing new alternative methodologies, established laboratories participating in validations and performing routine *in vitro* studies, and industry laboratories intending to submit *in vitro* data to regulatory agencies. These diverse types of institutions have different capabilities for developing and instituting quality systems that adhere to published recommendations while also suiting the unique operational environment of their facilities. This poster shares a practical strategy for using the GIVIMP document to assess current laboratory processes and increase the reliability and robustness of work performed within a facility. GIVIMP has been used to prioritize areas of focus for building new and expanding existing good quality practices within the laboratory. It is hoped that through these laboratory quality improvements, data, reports, and manuscripts will be more scientifically robust and lead to increased reproducibility of *in vitro* work.

INTRODUCTION

GIVIMP is internationally recognized and was officially adopted by the Organization for Economic Cooperation and Development (OECD) as a Guidance Document in 2018 (OECD, 2018). It is anticipated that validation bodies and regulatory agencies will expect adherence to GIVIMP to ensure that the proposed method is fit for validation and ultimately regulatory acceptance. Additionally, data reviewers (e.g., companies and regulatory agencies responsible for product registrations) will have increased confidence in data generated in laboratories adhering to GIVIMP standards (Bas et al., 2021). However, given the breadth and depth of GIVIMP, it may be difficult and/or time consuming for researchers and in vitro laboratories to implement.

The Institute for In Vitro Sciences (IIVS) has operated a GLP compliant laboratory since its founding 25 years ago. IIVS quality assurance professionals, laboratory scientists, and test facility management determined that the quality of work performed at our facility would be strengthened by adhering to the GIVIMP recommendations, since GIVIMP contains critical elements to maintain reliable and reproducible results for *in vitro* methodologies that are not present within the GLP quality framework (OECD, 2004).

APPROACH

1. GIVIMP recommendations were grouped into topic areas that aligned with the chapters of GIVIMP: 1) Roles and Responsibilities, 2) Quality Considerations, 3) Facilities, 4) Apparatus, Materials, and Reagents, 5) Test Systems, 6) Test, Control, and Reference Items, 7) SOPs, 8) Performance of the Method, 9) Reporting of Results, and 10) Record Retention.
2. Within each chapter, items were categorized as either **Facility Related** or **Method Specific**.
3. Not all recommendations were applicable to the IIVS laboratory and the methods we are currently performing.
4. Adherence to GIVIMP recommendations was assessed by a QA professional.
   - 4.a. For facility related recommendations, Laboratory Management and/or Facility Management were consulted where processes and procedures needed to be put in place or modified.
   - 4.b. For method specific recommendations, scientists responsible for the performance of the method and/or Laboratory Management were consulted where processes and procedures needed to be put in place or modified.
5. Some solutions summarized in the table were already in place. Some were new processes.
6. The next step will be an assessment of the facility's adherence to GIVIMP by an external party.

Example: How **GIVIMP** recommendations can be used to **improve** a laboratory's **quality systems**

Take a photo for a pdf download of the full poster

RECOMMENDATIONS

- Assessing practices against GIVIMP is worthwhile for a laboratory, even if it is already compliant with Good Laboratory Practices (GLPs) since there are useful recommendations in GIVIMP that are not discussed in GLPs or other regulations and quality systems guidances.
- Partner with a quality assurance or quality system professional where expertise is lacking.
- Work through GIVIMP one topic area at a time and collaborate throughout the facility with the individuals responsible for each functional area.
- Consult test guidelines and affiliated protocols for method specific considerations where available. Where there are differences between laboratory procedures and these documents, the differences can be specified in the method Standard Operating Procedures (SOP)s and study plans.
- Consider the type of evidence you are creating to show proof that you are following GIVIMP as you are assessing your systems and creating new processes.
- Review of your program by an external party can provide an unbiased check against the GIVIMP recommendations.

REFERENCES

Bas, A., Burns, N., Gulotta, A. et al. (2021) "Understanding the Development, Standardization, and Validation Process of Alternative In Vitro Test Methods for Regulatory Approval from a Researcher Perspective". *Small.* 22 January 2021. https://doi.org/10.1002/smll.202006027

OECD (2004),"The Application of the Principles of GLP to in vitro Studie", OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 14, OECD Publishing, Paris, https://doi.org/10.1787/9789264084971-en

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

The solutions presented in the table below are examples that work for our laboratory within the context of our programs. The same solution applied in the context of a different laboratory's programs may not satisfy GIVIMP recommendations.

GIVIMP Recommendation	Facility or Method	Topic Area	Applicable Individuals	Solution
2.5. Are all consumables and reagents evaluated against fit for purpose?	Method	Apparatus, Materials, Reagents	scientists, lab management, QA	Standard consumables and reagents are specified, including suppliers, in the method SOP.
				Where the consumable or reagent has not been identified as "critical", "or equivalent" is written into SOPs and study plans to signify that it is acceptable to substitute similar reagents when the standard specified is unavailable.
				Study documentation routinely includes the supplier of the consumables and reagents used.
2.6 Is there a formal staff training program	Facility	Quality Considerations	laboratory management, QA, scientists, staff	The onboarding process includes training on facility topics like quality systems, general documentation practices, computer use, and method specific techniques.
				Training files have been established to hold documentation of this training. For technique training, a senior staff member with demonstrated proficiency in the technique is responsible for documenting that the trainee is authorized to perform the work independently.
2.8 Are individual user names and passwords used to allow for proper attribution of electronic data?	Facility	Apparatus, Materials, Reagents	scientists, lab management, IT, QA	An inventory list includes all software in use for data collection and manipulation in the laboratory.
				All data collection software is assessed to assure individual log-ons are required and that the system captures information on the generation of the data record at a minimum.
				Where the software used does not include access controls or attribution, additional documentation procedures such as recording data processing in the paper workbook are used and data processing spreadsheet access is limited.
2.8 Are there controls around data processing	Method	Apparatus, Materials, Reagents	scientists, QA	Data processing procedures, including formulas, are defined in the method SOP.
				For efficient analysis of data from standard methods, data processing templates are created and locked to editing to protect formulas.
				Where routine processing is not possible, quality control checks of calculations are put in place.
3.3 Are bacteria and yeast activities separated from cell and tissue culture work	Facility	Facility	laboratory management, QA	This requirement is not applicable. No bacteria or yeast activities take place at IIVS.
3.3 Is there a prescribed workflow to prevent cross-contamination and is it followed?	Facility	Facility	laboratory management, QA	Sterile cell and tissue culture work is performed in the biological safety cabinets in a designated area of the laboratory. *Ex vivo* tissue and non-sterile work is performed in a different area of the same laboratory.
4.2 Are materials and reagents from well established sources?	Facility	Apparatus, Materials, Reagents	laboratory management, facility management, individuals responsible for ordering supplies, QA	Material and Reagents are divided into two catagories: critical (those vendors which provide specific products essential to the proper conduct of the study and whose quality or performance might reasonably be expected to affect the quality of the study as determined by laboratory and facility management) and standard.
				Critical vendors and suppliers are assessed as part of a company wide critical vendor and subcontractor audit program every two years.
				Standard suppliers are identified for the remaining, non-critical, materials and reagents to expedite laboratory ordering. Suppliers are identified in SOPs and study plans and "or equivalent" is used to indicate that the specified supplier does not have to be used.
6.1 and 6.11 Are there limitations based on the appearance, color, or physicochemical characteristics of the test item?	Method	Performance of the Method	scientists, QA	Limitations of the method, including test item types and chemistries that would adversely affect the method endpoint or other method step, are defined in the method SOP.
				Training is provided to new scientists and laboratory staff on the method that includes discussion of potential test item interferences and any mitigation strategies.
6.2 Is the applicability domain of the method explained?	Method	Performance of the Method	scientists, QA	SOPs are reviewed to assure that the "Scope" and "Purpose" sections describe the applicability domain.
				Study Plans are reviewed to assure the "Purpose", "Test System" and "Experimental Design and Methodology" sections, together, describe the method's applicability domain.
6.2 Are the limitations and exceptions of the method explained	Method	Performance of the Method	scientists, QA	SOPs are reviewed to assure the "Scope" and "Purpose" sections describe any limitations and exceptions of the method.
				Study Plans are reviewed to assure the "Purpose", "Test System" and "Experimental Design and Methodology" sections, together, describe any limitations and exceptions of the method
6.4 Are an adequate number of concentrations tested for the test item?	Method	Test, Control, Reference Items	scientists, QA	For OECD TG Methods - The test guidelines specify the number of concentrations to be tested for dilution based assays.
				For newly transferred methods without test guidelines: SOPs, study plans, and published literature on the method are referenced to determine an appropriate number of concentrations of the material to start with. The end point is flagged for assessment during future optimization efforts.
8.1 Have acceptance criteria been established for the method? How have they been determined?	Method	Performance of the Method	scientists, QA	For OECD TG methods - acceptance criteria are defined by the guidance document and transferred to method SOPs and study plans.
				For newly transfered methods - study plans indicate that the acceptance criteria are under development. The criteria for determination of a valid test in the study plan lists general criteria such as concurrance between replicates or number of values needed over a defined threshold, or the statistical model to be used for determining statistical significance of the results.

NOTE: Items above in bold italics are not requirements within the Good Laboratory Practice regulations.