

Letter

How a GIVIMP Certification Program Can Increase Confidence in *In Vitro* Methods

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Regulatory bodies, validation authorities, method developers, and industry toxicologists realize the need to increase confidence in the scientific validity of novel *in vitro* methods – especially those being proposed for regulatory application (Patterson et al., 2021). While the demand for these new methods is increasing, many methods that are proposed for validation or regulatory consideration have been found to need significant improvement¹ before they can be properly evaluated – thus resulting in delays, or even failures, in the acceptance process. This problem led the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) to coordinate a group of international experts to define standards unique to the development and execution of *in vitro* methods. The resulting Organization for Economic Cooperation and Development (OECD) guidance document, Good In Vitro Method Practices (GIVIMP) (OECD, 2018), stands as a comprehensive quality framework that provides recommendations for all stages of an *in vitro* method's life cycle: from development and validation to acceptance and use in the generation of data for decision-making.

GIVIMP is internationally recognized and was officially adopted by the 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. Also, 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. To overcome these challenges, the Institute for In Vitro Sciences (IIVS) has developed a GIVIMP Certification Program which will provide guidance on implementation of the quality principles. Participation in the program will demonstrate adherence to essential quality standards and will

build confidence in the method developer, the method itself, and the laboratories performing it.

Why use GIVIMP for quality standards?

Good Laboratory Practice (GLP) (OECD, 1998) and Good Cell Culture Practice (GCCP) (Coecke et al., 2005; Pamies et al., 2020) provide important topics to consider, but neither serves as a comprehensive quality framework for the development or execution of *in vitro* methods. Although GLP's focus on the reproducibility of non-clinical studies is important, its requirements do not always fit *in vitro* methods (Cooper-Hannon et al., 1999), and critical elements to maintain reliable and reproducible results for *in vitro* methods are missing (OECD, 2004). Similarly, while GCCP guidelines provide reference for designing and implementing procedures for cells and tissues, they do not include full method (i.e., assay) specific concerns. GCCP guidelines also do not ex-

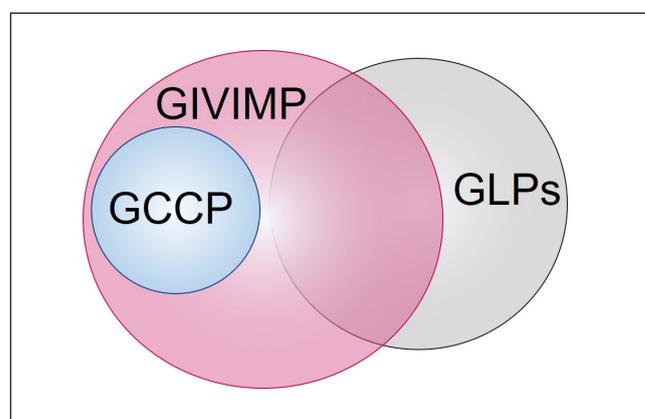


Fig. 1: GIVIMP incorporates the relevant elements of the GLPs and GCCP, however not all recommendations are applicable to every test method, developer or laboratory

¹ <https://ec.europa.eu/jrc/en/science-update/international-guidance-good-practice-development-and-application-vitro-methods> (accessed 24.02.2021)

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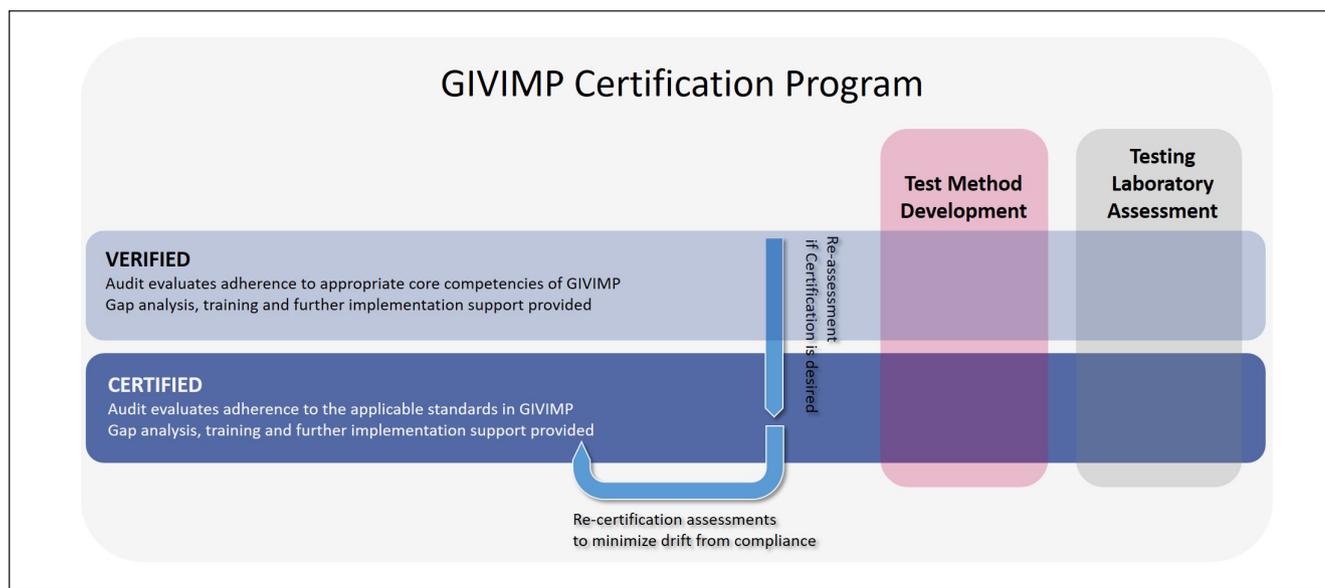


Fig. 2: The IIVS GIVIMP Certification Program assists test method developers and laboratories routinely conducting *in vitro* work to implement the standards of GIVIMP

tend themselves to those methods where parts of a cell or cellular products (e.g., RNA) or *in chemico* systems are the test system. Results of these types of methods are often analyzed in conjunction with cell-based methods, such as in a defined approach for skin sensitization (Urbisch et al., 2015); therefore, a framework which addresses these test systems is preferred.

GIVIMP incorporates the relevant elements of both GLP and GCCP (Fig. 1) and includes guidance on the execution of the entire test method including the use of reference materials and the determination of appropriate acceptance criteria for the method/assay. While a broad range of topics is covered within the guidance, not all recommendations are applicable to every developer, method or laboratory. Working with a knowledgeable partner to help navigate the guidance and implement the appropriate components of GIVIMP would be advantageous.

How a certification program will help implement GIVIMP

While GIVIMP is recognized as internationally harmonized guidance, it is not a regulatory standard and thus no government authority is responsible for overseeing the implementation of its recommendations. It is up to the *in vitro* community to harmonize both the interpretation and implementation of GIVIMP so that claims of compliance are understood to be uniformly meaningful. It is also incumbent on this community to ensure that the important principles contained in this document are not overlooked but rather put into practice by the intended audience. The IIVS Certification Program will not only provide this harmonization; it will also be a meaningful process for participants that

results in practical benefits for both the method developer and data user. GIVIMP, inclusive of its Annexes such as the GCCP, is a 260-page document spanning a range of topics intended to promote quality during a method's life cycle. Not all guidance is applicable to every method and laboratory. Researchers new to quality frameworks and even experienced laboratories (e.g., those certified for GLP and/or ISO standards) will spend resources to determine the most relevant principles to follow and the best course to implement them. A certification program that provides guidance on which standards to prioritize and recommendations on how to achieve compliance transforms the sizeable GIVIMP guidance into a manageable, systematic approach for improving laboratory processes and creating a quality framework.

The IIVS is a non-profit organization with a mission to increase the use and acceptance of *in vitro* methods worldwide. As a GLP-compliant laboratory, IIVS is familiar with auditing and applying quality standards to *in vitro* methods. Recently IIVS was part of a consortium to create e-learning modules on developing reliable and relevant alternative non-animal approaches for regulatory use. The project, sponsored by the European Commission (Zuang et al., 2019), presents an interactive summary of GIVIMP concepts. IIVS combined its technical understanding of *in vitro* methods with its quality and auditing expertise and has created a GIVIMP Certification Program that supports its mission and serves the *in vitro* community at large.

To help select the key elements of the Certification Program, IIVS collaborated with the Experimental Toxicology and Ecology laboratory and quality assurance group of BASF SE. As an experienced developer of *in vitro* methods, a GLP- and ISO-compliant testing facility, and an EU Netval² laboratory, BASF has

² <https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/eu-netval> (accessed 24.02.2021)



a long history of compliance with, and utilization of, quality frameworks. As a large commercial entity, BASF faces the challenge of assessing multiple new methods per year as well as reviewing *in vitro* data generated by a number of laboratories. Adherence to the principles in GIVIMP provides the data user confidence in the new methods and generated *in vitro* data.

The key elements or “core competencies” of the program have been identified for each of the areas covered by GIVIMP. These core competencies are applicable to both the development of a single method and the overall organization of laboratory operations. When a laboratory demonstrates adherence to these core competencies, they will be considered “GIVIMP Verified” for the facility or the method(s) assessed. When additional criteria that go beyond the core competencies are implemented, they will be considered “GIVIMP Certified.” The verification and certification assessments are intended to support a laboratory’s evolving standards of quality and increasing compliance with GIVIMP recommendations over time. It is not a single point assessment leading to a pass/fail determination, rather a process to assist in understanding and implementing the standards (Fig. 2).

The structure of the GIVIMP Certification Program is flexible so that it is feasible for all sizes and types of *in vitro* laboratories. Small and large facilities, academic laboratories, contract research organizations, governmental and industry laboratories can all participate in, and benefit from, the assessment process. After assessment by a qualified auditor assigned by IIVS, each facility will be provided with a comprehensive report of their processes compared to GIVIMP. If after an assessment a laboratory is not ready for verification, their report will provide specific recommendations to improve adherence to the standards. Re-assessment can be conducted once the facility has had time to follow the recommendations. This process assists smaller laboratories with limited resources or experience to participate in the program and improve their quality framework in a managed way. Participation in the program can be an important step toward structuring, and continuously improving, laboratory processes. With periodic re-assessments to maintain certification, laboratories will be alerted of any drift from compliance and updated on application of GIVIMP to regulatory and technological advancements.

Summary

IIVS GIVIMP Certification confirms the high-quality work performed at a facility and communicates commitment to excellence in *in vitro* laboratory work. The GIVIMP Certification Program gives structure and consistency to the application of GIVIMP standards and assists laboratories to apply them. Without such a certification program, claims of successful application of GIVIMP will be left to individual interpretation, which could lead to erosion of the concepts and intent of the documented standards – or even to the abandonment of these important principles and their intended benefits for the *in vitro* community.

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Conflict of interest

Amanda Ulrey and Erin Hill are employed by the Institute for *In Vitro* Sciences, Inc., a non-profit organization that will charge a service fee to support this certification program.