Abstract #422

Key Recommendations from GIVIMP for Test System Suppliers

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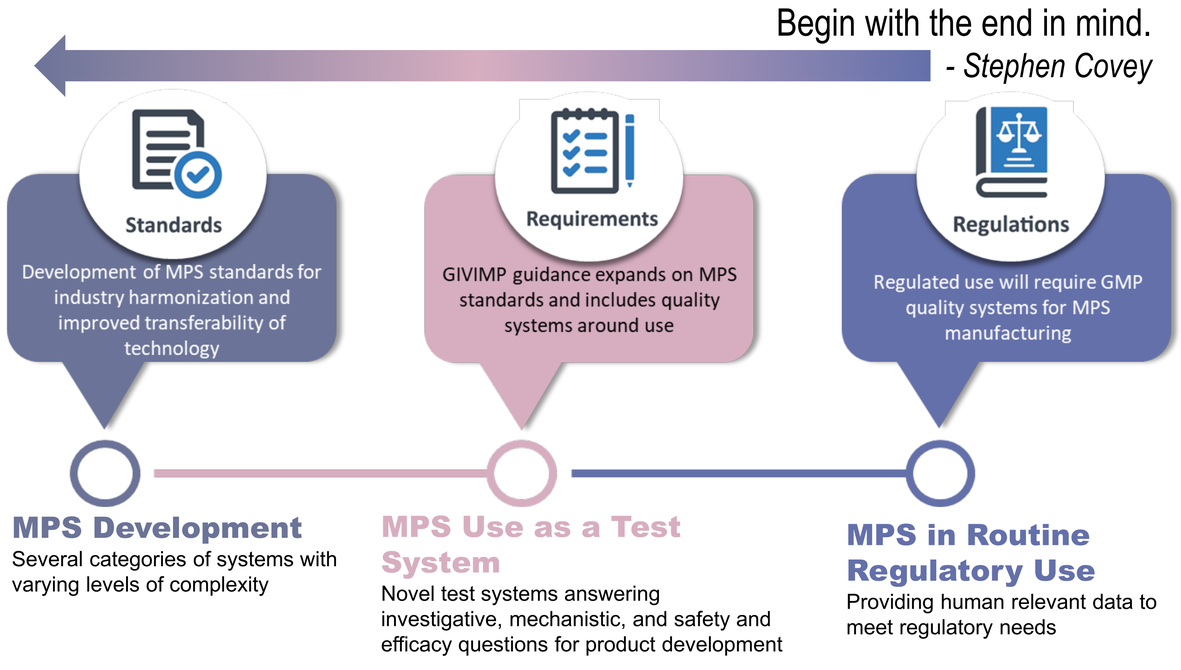
ABSTRACT

The Organization for Economic Cooperation and Development (OECD) guidance document on Good In Vitro Method Practices (GIVIMP) details a set of quality standards to improve both the quality of and confidence in newly developed, and routinely executed *in vitro* methods. An important part of (and a source of potential high variability in) any method is the test system. Microphysiological Systems (MPS), including organ-on-a-chip platforms have been used in novel methods for many years. Despite their potential benefits, there are several quality concerns associated with MPS. Two of these concerns are reproducibility and well defined and understood biological relevance, both of which are covered in the GIVIMP guidance. GIVIMP provides recommendations and points to consider intended to help improve the quality of the test systems used in *in vitro* methods. It is important that these MPSs align with the recommendations in GIVIMP to help support the reproducibility and relevance of the methods that use these test systems. Providers of commercial MPS like 3D tissue culture and organ on a chip systems as well as research labs creating and using MPS systems internally can reference the GIVIMP guidance as they set up processes and procedures to routinely prepare their systems for testing use.



Quality and Standardization of MPS Test Systems

The need to standardize the structure, function, and use of MPS is widely understood and supported. Several organizations and societies, like the JRC, the European Committee for Standardization (CEN), and the European Committee for Electronical Standardization (CENELEC), and the European Organ-on-Chip Society (EurOoCS) are already working together to standardize the science behind MPS (Piergiovanni, 2021). These efforts are helping to set the stage for characterization of MPS for use as test systems with an ultimate goal of making them more accessible for use in areas of science beyond research and development.

Standardization of the design elements and functional parameters of MPS paves the way for the establishment of quality systems around their construction and use. Following quality systems assures that the MPS is behaving as expected in a variety of contexts. Whether the MPS manufacturer is performing routine work or a small laboratory is using the MPS in a novel way, the standards and acceptance criteria defined by the quality system for the MPS will create evidence that the system is fit-for-purpose and performing within acceptable limits and in a way that is comparable to past performance. Rather than putting limits on MPS use, these standards and quality guidelines will allow for faster uptake of these test systems across a variety of laboratories in a way that disseminates their use while protecting the integrity of MPS itself.

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 is divided into 10 chapters addressing the topics shown in the image 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.

Point to Consider from GIVIMP for MPS Test Systems

Chapter 1: Roles and Responsibilities

- Suppliers should provide test system users with adequate information to properly operate and use the system.
- There should be documentation that test system characterization has been met.
- Supplier should provide documentation of sterility.

Chapter 2: Quality Considerations

- Control charts (positive, negative, or reference items) can be used to demonstrate performance within acceptable limits.
- Is testing performed to determine a batch/lot is within these acceptable limits and the results communicated to test system users?
- Is special training or certification needed to use the MPS?

Chapter 3: Facilities

- Are the laboratory requirements for proper MPS use defined and communicated (including BSL level, power, etc.)?
- Are there any safety risks to be addressed?
- Have acceptable disinfectants and cleaning procedures been described to users?

Chapter 4: Apparatus, Materials, and Reagents

- Have individual components of the MPS or the MPS functionality as a whole been evaluated against fit-for-purpose?
- Are there defined quality checks for the system or consumable components?
- Have acceptance criteria been defined for the MPS or are consumable components subject to wide variability?
- Is a computerized system used to control aspects of the system and, if so, are settings and actual run data captured and saved?
- Is the MPS compatible with a variety of types of equipment or is specialized, specific equipment needed?
- Are acceptable operating limits set, monitored, and recorded?
- Is equipment fit for purpose regarding sensitivity and selectivity?
- Is the MPS performance calibrated or verified prior to use? Has the system undergone formal validation?
- Is there a recommended maintenance schedule?
- Is there a recommended media to use as part of the MPS? If so, does it contain sera or is it chemically defined?

Chapter 6: Test, Control, and Reference Items

- Where reference items and controls are used to show proper performance of the MPS, are they appropriately characterized and are records of identity retained?
- Is reference data published so that it can be referenced by all MPS users?
- Is it likely that there are classes of materials that will have unintended effects on the MPS system?

Chapter 7: SOPs

- Are methods for MPS production and use standardized and documented (in SOPs)?
- Are deviations from SOPs documented?
- Were methods standardized prior to performing validation activities or setting performance criteria?

Chapter 10: Record Retention

- Are documents related to the MPS test system retained?
- Does record keeping follow the principles of data integrity?
- Does the system produce metadata and is it retained?

Chapter 5: Test System

- Are the cells, tissue constructs, organoids, or tissues provided as part of the MPS? If so: are they obtained from a certified provider, is there characterization documentation and documentation of absence of contamination (such as mycoplasma), and has the biological material been obtained ethically?
- Are procedures in place for maintenance of the MPS, including the biological components?
- Where cell lines are used, is there proof that the cells are free of cross contamination?

Chapter 9: Reporting of Results

- Where elements of the MPS are covered by Intellectual Property Rights (IPR), there is guidance for providing generic descriptions of those components.
- Are performance standards, use instructions, and historical reference and control items ranges communicated to users
- Is there a preferred way for reporting performance?
- Are critical reagents and equipment used during manufacturing recorded?

Defining the Test System

Test systems are defined as the biological, chemical or physical system or combination thereof used in a study. GIVIMP notes the following concerning test systems:

> "As *in vitro* test systems become more sophisticated, the definition of the test system will need to cover the biological, chemical, or physical system in the finalized platform to be used for testing ." (OECD, 2018)

It is critical for MPS that the entire system (cells, pumps, incubators) is considered to be the test system. The system must be functioning correctly as a whole in order for any data produced to be considered reliable; therefore, all components must individually meet established performance standards in order for the test system to be deemed acceptable for use. Quality systems should be implemented for each component of the test system to assure the reliability of the overall function of the MPS test system.

References

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