Scope

The major goal of GIVIMP consists of improving 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. The scope of the GIVIMP guidance, taking into account good scientific, technical and quality practices, is to ensure that the overall process, starting from *in vitro* method development to the final *in vitro* method implementation for regulatory use is more efficient and effective.

The document emphasis is mainly on human safety assessment using mammalian cell and tissue cultures. It may, however, be broadened to other fields such as environmental safety assessment, gene therapy and immunology domains. It is mainly focused on more commonly used 2D cell and tissue culture systems, but may also be applied to other test systems such as 3D cultures, whole organ systems etc. (Fennema et al., 2013[1]); (Matsusaki, Case and Akashi, 2014[2]).

The document applies mainly to current test systems, practices, trends and processes. If and when felt relevant the WNT will be tasked with issuing a new version. In the various chapters different types of 2D and 3D test systems (cell lines, co-cultures, primary cells, stem cells and tissue cultures) have been provided as examples, however it should also be stated that there are still some reliability issues with the use of some of these test systems for current regulatory testing (e.g., the current "irreproducibility epidemic", challenging scientific questions related to 3D systems) (Frye et al., 2015[3]). Therefore, there was a consensus amongst the OECD GIVIMP expert group that some of the more complex test systems may not yet be at the level required for use in the OECD test guidelines programme, however they may be accepted in the future when the reliability issues are worked out.

In this guidance the OECD Good Laboratory Practice (GLP) term test item is used, where possible, since its applicability ranges from pure substances, mixtures, multi-constituent substances to other types of test items (e.g., nanoparticles, medical devices).

This guidance document targets all players involved in the process, e.g., *in vitro* method developers, *in vitro* test system producers, validation bodies, producers of equipment, materials and reagents, *in vitro* method users, testing laboratories, large industries and small to medium enterprises as well as receiving authorities, monitoring authorities, accreditation bodies and the OECD. The guidance aims to further facilitate the application of the OECD Mutual Acceptance of Data (MAD) agreement to data generated by *in vitro* methods and as such contribute to avoiding unnecessary duplicate testing. This guidance describes the areas related to *in vitro* method development, standardisation, harmonisation, and international acceptance that would benefit from more detailed scientific, technical and quality guidance.

The GIVIMP document has been written with different users in mind, including GLP test facilities but also research laboratories developing new *in vitro* methods. In the latter

case, full compliance with GIVIMP may not be realistic, but compliance with as many as possible of the "good practices" will facilitate the acceptance and routine use of the *in vitro* method in a regulatory environment.

GIVIMP is not intended to duplicate or replace existing OECD guidance or advisory documents but is complementary, addresses specific gaps and aims to collect available references and information on best scientific, technical and quality practices in one document.

GIVIMP is divided into ten sections covering:

1. Roles and Responsibilities
2. Quality considerations
3. Facilities
4. Apparatus, material and reagents
5. Test systems
6. Test and reference/control items
7. Standard operating procedures
8. Performance of the method
9. Reporting of results
10. Storage and retention of records and materials

At the beginning of each chapter a summary box with the key message, key content, guidance for improved practice, and recommendations is included. Abbreviations are repeated per chapter since some readers might read only one chapter, i.e. each chapter may be considered as a separate document. Abbreviations are presented in full at the first occurrence per chapter, For the remainder of the chapter only the abbreviation is used.

Throughout this document, the word *must* is used to denote an obligation; instances of *must* are also often specific to particular context. We use the word *should (be)* to convey a recommendation and that there may exist valid reasons in particular circumstances to disregard the recommendation, but the full implications must be understood and carefully weighed (and documented). The word *may (be)* is generally used to convey an advice and is as such truly optional.

References

Fennema, E. et al. (2013), "Spheroid culture as a tool for creating 3D complex tissues", *Trends in Biotechnology*, Vol. 31/2, pp. 108-115, http://dx.doi.org/10.1016/j.tibtech.2012.12.003. [1]

Frye, S. et al. (2015), "Tackling reproducibility in academic preclinical drug discovery", *Nature Reviews Drug Discovery*, Vol. 14/11, pp. 733-734. [3]

Matsusaki, M., C. Case and M. Akashi (2014), "Three-dimensional cell culture technique and pathophysiology", *Advanced Drug Delivery Reviews*, Vol. 74, pp. 95-103. [2]