Chapter 7. Standard operating procedures

Key message: *Standard Operating Procedures (SOPs) and the accompanying forms, templates or worksheets should be written and prepared in a way that they will form the tools to simplify the work of the user when carrying out an in vitro method study.*

Key content: *The chapter elaborates on the correct documentation of in vitro methods for routine testing including requirements for clear and concise SOPs.*

Guidance for improved practice: *The evolution of a non-routine in vitro method to a routine in vitro method is described in a step-wise manner.*

Recommendations *to derive a set of clear, well-written in vitro method SOPs are given.*

According to the OECD Principles of Good Laboratory Practice (GLP) (OECD, 1998[1]), Standard Operating Procedures (SOPs) are defined as documented procedures which describe how to perform testing methods or activities normally not specified in detail in study plans or Test Guidelines (TGs). Formal SOPs facilitate consistency in the quality and integrity of a product or end-result, and are required by GLP. SOPs may include testing methods, instructions, worksheets, and laboratory operating procedures. SOPs are essential in a quality management system and must be formally authorised by management in a GLP test facility.

The aim of SOPs is to ensure that procedures are carried out in a consistent and reproducible way by qualified personnel. Therefore SOPs need to describe, in sufficient detail, clear work instructions for a trained user to minimise the risk for misinterpretation.

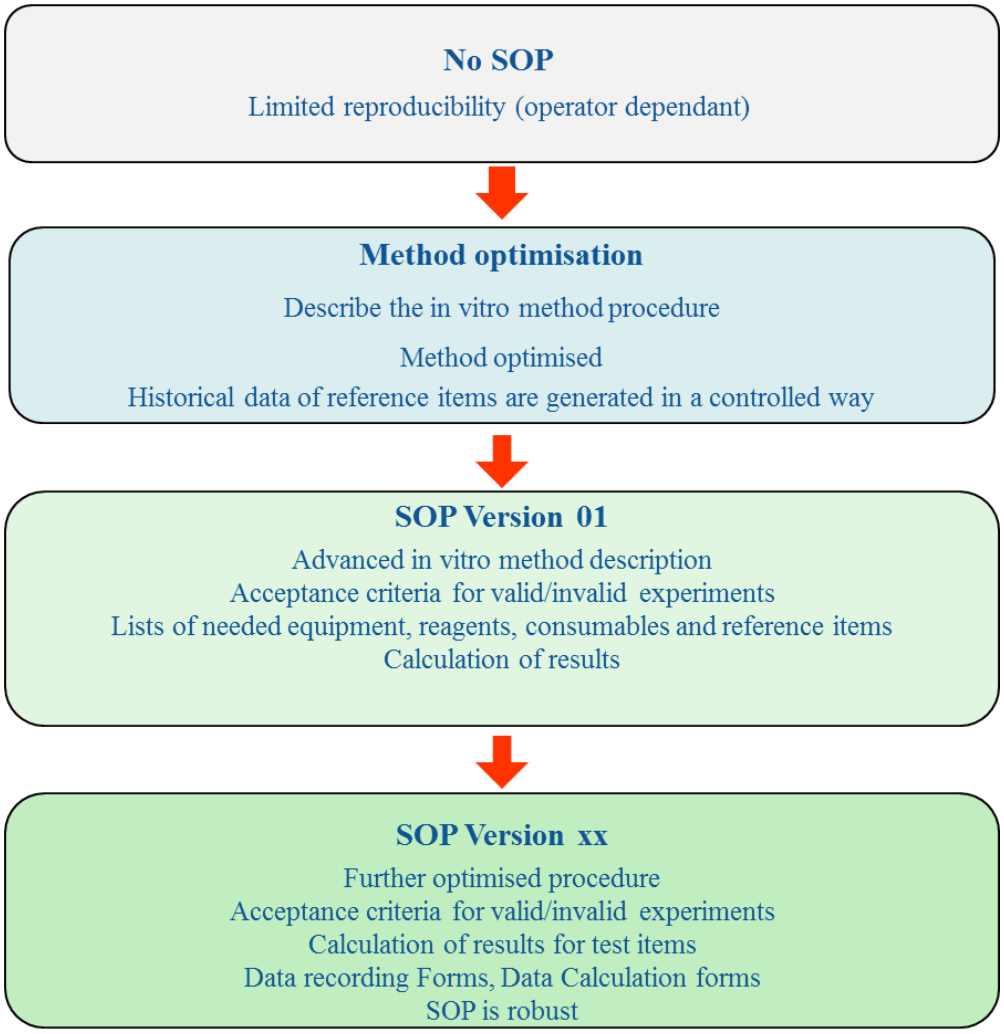
An *in vitro* method will be supported and documented with a number of different SOPs, forms, templates and worksheets. Besides the description of the main test procedure, SOPs for supporting procedures (e.g., the handling of cell cultures, waste handling, cleaning procedures, operating and calibration instructions for the equipment, record keeping, reporting, archival, quality assurance procedures, etc.) need also to be available and used. To avoid lengthy documents, the instructions are preferably divided into a series of SOPs. The SOPs must be readily available to personnel in each working area.

7.1. *In vitro* method standard operating procedures development

The development of an in vitro method for regulatory testing purposes is a difficult and time-consuming task. In the initial stages of the development, the procedure will undergo many changes and each step needs to be described in laboratory records, which will crystallise into laboratory procedure(s) or a set of SOP(s) along the test development process. During this period a historical dataset on the reference and control items will also be collected. This dataset will be used to define the critical and relevant end-parameters and the control and reference items acceptance criteria.

Once the method is sufficiently developed and all parameters are defined, an in-house validation process during which the *in vitro* method is assessed for repeatability (accuracy & precision), selectivity, sensitivity, and stability should be performed (Section **8.3**). Likewise, its robustness is assessed (i.e., the influence of (external) parameters on the outcome parameters), as it is important to ensure the *in vitro* method performs in different laboratory environments, albeit within defined boundaries.

Figure 7.1. Evolution of a Standard Operating Procedure (SOP)



Optimisation of the SOP should be performed by following a formal procedure prior to formal in-house validation. It is critical that any parameter(s) to be optimised should be chosen prior to the optimisation process, should be measurable, so as to allow before and after comparison, and should include the optimisation steps to be performed. All data acquired during the optimisation steps should be annotated to allow tracking, comparison and measurement of the acquired optimisation.

During the in-house validation process (Section 8.3), weaknesses can come to light that may require adaptation or optimisation of the method, and which might also trigger the re-initiation of a new validation cycle. It is recommended that any intended changes introduced during the validation should be in the form of amendment(s) to the validation plan.

In addition, the *in vitro* method developer should be aware that if the *in vitro* method makes use of complex instrumentation and software, these commercial off-the-shelf products will require appropriate validation depending on the risk and the complexity of any customisation (OECD, 2016[2]). Spreadsheet templates using pre-defined formulas,

self-written equations, or macros developed for use with the *in vitro* method must also be validated and will also require documented procedures for correct use.

Upon a satisfactory completion of the validation process, the *in vitro* method development can be finalised and the final set of SOPs associated with the *in vitro* method will be available.

Once an *in vitro* method has been validated and published, e.g., in the format of an OECD Test Guideline (TG), the users will, from the published method, need to develop their own set of SOPs which are applicable and integrated into their organisation to assure the correct execution of the *in vitro* method within their facility's environment.

7.2. Preparing standard operating procedures

As indicated above, how to perform the *in vitro* method and related procedures is given in a set of SOPs, covering how to execute the *in vitro* method but also SOPs referring to general supporting procedures (e.g., test system handling, solubility assessment, cytotoxicity measurement, equipment maintenance, calibration and cleaning; handling of test and reference items; record keeping, reporting, storage, and retrieval, etc.). The reason for not having all *in vitro* method steps and processes described in one single SOP, but in a set of SOPs is for ease of use by the personnel involved and for facilitating regular review and updating.

The OECD GLP Principles (OECD, 1998[1]) provide examples of activities and processes that should be described in SOPs, while additional examples specific to *in vitro* testing are listed in the OECD advisory document on The Application of the Principles of GLP to *in vitro* Studies (OECD, 2004[3]).

SOPs should be written in the active voice and concisely explained in a step-by-step procedure, easy-to-read format. The information presented should be unambiguous and not overly complicated. The document should not be wordy, redundant, or overly lengthy but simple and short. The inclusion of a flow chart and/or a checklist to illustrate the process can help to make it clearer and more easily executable.

SOP(s) are best written by the individual(s) actually performing the work on a daily basis. The finalised SOP needs to be reviewed and approved by laboratory management, or the test facility manager in a GLP environment. SOPs are not static documents and need to be systematically reviewed on a periodic basis. SOP(s) may also need to be adapted whenever something changes (e.g., products, equipment and facility). In these cases a new version of the SOP should be approved. As soon as a new version is approved (date of approval), all concerned personnel need to be informed and the obsolete version removed from use and adequately archived. To allow and control this, all SOPs need to have a unique identifier (Title/version number/approval date). It is also recommended to detail the revision history in the document. In a GLP facility SOPs should be formally authorised by test facility management.

It is a good policy to divide SOPs by type, e.g., the EPA Guidance for Preparing Standard Operating details two types, technical SOPs and administrative SOPs. The guidance document provides examples and a standard layout for both technical and administrative SOPs (EPA, 2007[4]).

References

EPA (2007), *Guidance for Preparing Standard Operating Procedures*. [4]

OECD (2016), *Application of Good Laboratory Practice Principles to Computerised Systems*, OECD Series on Principles on Good Laboratory Practice and Compliance Monitoring, No. 17, OECD Publishing Paris. [2]

OECD (2004), *The Application of the Principles of GLP to in vitro Studies*, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 14, OECD Publishing, Paris, http://dx.doi.org/10.1787/9789264084971-en. [3]

OECD (1998), *OECD Principles on Good Laboratory Practice*, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 1, OECD Publishing, Paris, http://dx.doi.org/10.1787/9789264078536-en. [1]