Standard Operating Procedure

Title: Method Validation Master Plan

Department	Validation/Technical Services		Document no	VAL-240	
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

Table of Contents

The MVMP does not cover equipment qualification which is covered in the site Validation Master Plan (VAL-080) or method development studies.

NB: This plan is a sub-plan of site Validation Master Plan (VMP) VAL-080 and must be read in conjunction with that plan. The VMP details the generic supporting quality systems such as training, validation approach, validation life cycle, management of validation items and validation studies, establishment of priorities and validation documents. For test method validation the same principles apply even though the terminology may differ. Abbreviated and / or method specific versions of certain contents of the VMP are included here to aid readability and understanding.

The plan will define [Enter Business name] approach to Method Validation. The objectives of the plan are to:

- Provide assurance that test methods support the continued supply of quality and safe products.
- Provide a risk based approach to Validation and the assurance of product quality.

The term "Validation" will be used throughout this document to describe activities undertaken to assure the compliance of test methods to the principles or regulations of GMP.

3 Regulatory Standards

[Enter Business name] agrees to comply with Good Validation Practices as define in [Enter list of Regulatory Standards]. Where additional guidance is required reference may be made [Enter additional Regulatory Standards].

4 Responsibility

[Enter Business name] will provide an appropriate level of competent resources to ensure the achievement of the outline Validation program, with consideration of the risk associated with the product.

4.1 Authority and Responsibility

The QC Manager(s) take overall responsibility for method validation. Responsibility for the execution of individual elements of the validation program will be determined by the QC Manager and Quality Manager.

Team members undertaking validation activities shall be appropriately trained and competent for each task undertaken. Review and approval of Validation activities and documentation should be conducted by Suitable Subject Matter Expert (SME) and / or Quality Assurance.

Activity	Protocol and Document Preparation	Protocol and Document Approval	EV Reports	MV Reports	Risk Assessment	Final Report Approval & Certification
Test Method Validation (MV)	Quality Control Validation	Validation Manager Laboratory Manager Senior Manager – (QO)	Considered a pre-requisite to Method Validation	QA/QC Validation	Cross Function Team including SMEs	Validation Manager Laboratory Manager Senior Manager – (QO)

4.2 Life Cycle Approach

It will be the intention of the Validation program to consider all stages of the life cycle to ensure all critical test methods are well designed, challenged appropriately, successfully maintained and

4.3 Management of Methods and Validation Studies (Projects)

4.3.1 Methods

Method validation records are stored in the Validation section of the Validation database and enable the tracking of validation status. Within the database the current status, planned and completed dates, area (location) and method type can be recorded.

4.3.2 Validation Studies (Projects)

Validation studies are undertaken to provide documented evidence that a test method that has a critical impact on product quality has been validated as designed, is compliant with GMP and appropriate for its intended use. The extent to which Validation studies are undertaken will be appropriate to the perceived risk level of the method under validation.

Within the Validation database Validation studies are assigned a unique project number are tracked within the Project section.

4.3.3 Risk Management

The key component to the [Enter Business name] MVMP is risk based assessment. Categorisation of risks, validation priorities and preparation of schedules, including timelines, are determined by a consultative process involving the QA Manager Systems and Department Managers.

Priority shall be given to the validation of new test methods and those methods deemed by risk assessment to be highly critical. Validation priorities shall be established using the risk-based matrix as noted in step 4.3.4.

4.3.4 Establishment of Validation Priorities for Test Methods

The following matrix has been designed to determine the priority for validation of test methods.

	Registered Products					
	New Products	Vaccine	Pharmaceutical	Antigens	Nutritional	Non Registered
Sterile Injectable	High	High	High	Medium	N/A	N/A
Non-Sterile Injectable	High	N/A	High	N/A	N/A	N/A
Sterile Other	High	N/A	High	N/A	N/A	N/A
Non-Sterile Oral	High	N/A	Medium	N/A	Low	Low
Non-Sterile Topical	High	N/A	Low	N/A	N/A	Low

Table 1: Risk Matrix (Methods)

At the completion of the assessment process the Method Validation assessment is updated (refer Section C) and the Method Validation Master Schedule is also updated (refer Section D).

Concurrent validation of a test method can only be performed if it is validation of an existing legacy test method or done in parallel with development of a new product. Concurrent validation studies will be approved by Quality.

Method development / optimisation (also referred to as commissioning) may occur before method validation.

5.5 Pre-requisites for Method Validation

Prior to execution of a Test Method Validation study, the following must be addressed, whenever applicable:

- The test method involved must be defined, including operational ranges, critical test parameters, and critical steps. i.e test method development and optimization must be completed and final reports approved (or in the case of a legacy assay the standard test procedure must be defined).
- The Method Validation Plan/Protocol must be developed and approved; specifying predetermined and supported acceptance criteria for each experiment prior to the initiation of the method validation.
- Equipment used in the validation studies must be qualified in compliance with the site VMP.
- Critical utilities used in the validation studies must be qualified in compliance with the site VMP.
- Computer systems used in the validation studies must be qualified in compliance with the site VMP (though it is noted that some aspects of computer system validation for test equipment may be inextricably linked to validation of the test method and will therefore be validated at the same time the method is validated)
- Critical instrumentation must be calibrated.
- Personnel involved with the execution of the validation study must be properly trained in the relevant procedures and validation protocol sections.

5.6 General Acceptance Criteria for Method Validation

The following general acceptance criteria should be evaluated for applicability for each method validation study:

- Acceptance criteria are chosen so as to be both necessary and sufficient to assess the validation of the Method. As much as possible, they should be measurable and not be procedural. If applicable, source documentation for acceptance criteria must be referenced.
- The acceptance criteria should encompass the requirements and specifications used to evaluate the validity of the method during day to day use.
- Intra-batch (i.e variability between different samples and / or reagents) and inter-assay (i.e. variability between same sample in separate assays) variability should be assessed whenever applicable.
- Deviations related to the execution of validation studies must be reported in a timely manner and, if necessary, investigated to determine the root cause. These deviations must be documented and resolved according to the deviation reporting procedure within the protocol.

As previously indicated, each validation study should be summarized in an approved report.

5.7 Validation & Qualification Projects

Current validation projects are noted in the Schedule of Test Method Validation Activities, refer section D.

Robustness	Capacity to remain unaffected by deliberate changes and / or variations in method parameters. (reliability and stability)

6.2 Compendia Based Methods

For [Enter Business name] compendial methods currently include recognised compendia such as the EP, BP and USP. In addition, for the purpose of defining validation requirements, test methods published by the TGA / USDA (i.e. 9CFR.) or other government bodies and the AOAC are considered the equivalent to compendia methods and, therefore, fall under the definition of a compendia-based method.

Compendia methods are considered validated but must be verified under actual conditions of use. The suitability of a compendia analytical method is verified by:

- Meeting the requirements for validation if stated in the compendia monograph.
- Meeting the requirements of controls in the compendia monograph.
- Demonstrating appropriate specificity (e.g., there is no interference in the method from any impurities, degradants, or excipients for the product).
- Demonstrating the ability to run the compendia method under actual conditions of use.

Changes to existing compendia methods may occur. An evaluation of the change(s) should occur, and recommendations should be made in regard to local activities and the need for verification testing.

6.3 Microbiological Methods

6.3.1 General

Sterility, non-viability and preservative effectiveness are the most common microbiological test methods used to determine vaccine quality. Methods should be validated against compendial requirements which often state the validation requirements.

It is noted that for microbiological assays the validation is often part of the assay development e.g. non-viability assay and therefore a separate validation post method development is not always required.

For sterility testing, this normally means demonstrating that the test media chosen can support the growth of various challenge microorganisms in the presence of the product and that the product is not growth inhibitory.

For non-viability testing this normally means demonstrating that the test media chosen is the most sensitive for the specific micro-organism that the inactivated product is derived from. This is generally a comparison between the manufacturing media or another recognized media that provides good growth conditions for the microorganism and that there is no interference to growth from the residual inactivant. During the test validation, a comparison between solid, liquid and subculturing should be considered.

Preservative effectiveness testing must be performed per compendial requirements. Microorganisms used for this test are determined by compendial requirements. Other strains may be included, based upon formulation and intended use. The inclusion of environmental isolates needs to be considered.

Alternative microbiological procedures, including automated methods, may be used, provided that they have been validated and have been proven to be equivalent or superior to the compendial or existing method.

A compendial assay, if there are stated validation requirements must be validated as per the stated compendial requirements.

When validating an animal based method, the extent of the validation required must be balanced with the animal welfare cost. Reference to scientific literature can be leveraged to avoid unnecessary duplication of in-vivo testing.

Safety or toxicity tests require injecting a certain dose of product into an animal and determining if the product is safe or toxic / non-toxic. Validation considerations would include ability to discern between toxic / non-toxic (or safe / unsafe) material, dilution variation (if applicable) and dose application variation, (Intravenous, Sub-cut, Intraperitoneal). Due to the high animal welfare cost of validating these assays, if a risk based assessment has been written (and approved by QA) documenting the logic of the test, the likelihood of a false pass and field impact and an argument not to validate then test will not be validated.

Challenge testing, by its very nature, involves a set of vaccinates and a set of un-vaccinated control animals. Simplistically, vaccinates must survive the challenge and control animals must die. As the method has built in controls that qualify the assay each time it is performed and the method has high animal welfare cost, challenge tests are generally not validated.

Antigen potency testing involves an unknown amount of toxin or toxoid that is combined with known amounts and values of antitoxin or antitoxin / toxin combination at various levels. An indicator is added which may be in-vitro (e.g. blood) or in-vivo (e.g. mice) on which excess toxin can exhibit its effect. These assays are considered immunological analytical assays and should be validated following the same principles used to validate any analytical method. NB: Based on a documented justification comparing benefit to animal welfare cost for in-vivo assays not all aspects may need validating.

Serum generation is part of a potency assay. The timing of maximum antibody generation in a test animal is normally not critical as the pass value for the product is assigned from the vaccination schedule and is linked to product efficacy trials or compendial instructions. The QC method must reflect the same timing period. The vaccination schedule can impact on whether there is a linear dose response in the animal. The vaccination schedule should be validated to demonstrate that a linear dose response occurs and that a sub potent vaccine can be differentiated from an efficacious vaccine.

In-vivo antibody assessment methods are immunological analytical assays and should be validated following the same principles used to validate any analytical method. NB: Based on a documented justification comparing benefit to animal welfare cost for in-vivo assays not all aspects may need validating.

6.5 Legacy Test Methods

Legacy test methods are defined as those methods in current use prior to the approval of the original of this MVMP and where a validation package is known not to exist. Validation of a legacy test methods follows the same principles as validation of new methods however test performance data may be extracted from existing historical records rather than repeating assays.

The validation scope for a legacy assay may be reduced based on a documented justification and review of the historical performance of the assay and assessment of known assay.

Legacy compendia methods (as defined in the MVMP) are deemed verified based on an history of successful use.

6.6 Technology Transfers

Qualification of the receiving laboratory must be completed before the test procedure is used to release commercial product. Management is to identify transfer team members from the participating laboratories (e.g., receiving laboratory and transferring laboratory). The transfer team members are responsible for managing the transfer and qualification process and to ensure that all activities meet the requirements of this MVMP.

The results of the validation and transfer experiments shall meet predetermined acceptance criteria to be considered acceptable. The following principles for test transfer to be followed:

- Experience with a Highly Similar Test Procedure can be used as justification of qualification when the receiving laboratory is using methodology that is scientifically similar to the test procedure which is already being performed by qualified analysts in the receiving laboratory.

- Experience with a Highly Similar Procedure may be applied to test procedures for potency and purity of the active ingredient when the following conditions are satisfied: (1) The test procedures have equivalent instrumental requirements and (2) The test article sample preparations are comparable.

7 Validation documentation

The [Enter Business name] Validation program uses two types of controlled documentation, System management or guidance documentation and evidence of compliance documentation. The level of documentation required will be defined based on the type of study, potential risk and complexity of the study.

7.1 System Management Documentation (SM)

System Management documents are defined as those documents that describe the management of a Validation system or those documents created to provide guidance on critical tasks (e.g. method validation master plan).

7.2 Evidence of Validation documents

Evidence of Validation documents are those documents that provide a level of assure that a method has been validated and is fit for its intended use.

- Validation protocols are developed specifying instructions for execution and pre-determined acceptance criteria. Studies are executed in conformity with the validation protocol. The objective of each protocol is to provide clear and complete instructions for the execution of a validation study.
- Validation data is collected, recorded, analyzed, and summarized with a conclusion in a Validation Summary Report. Any unexpected events encountered during the execution are documented and thoroughly investigated. Investigation reports are reviewed and approved prior to the approval of the Summary Report.

Assays may be validated in Process Development or R&D departments. Protocols follow scientific format and the outcome of each protocol is a scientific report. As test methods may be validated off site by other [Enter Business name] bodies (e.g. International R&D) documentation may differ in appearance from that used on site

