Total Pathway to Method Validation

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Introduction

The role of medical laboratory scientists in method development extends well beyond the customary bench practices of validation and verification towards involvement with the total process from conception to commission. There is a temporal sequence of activities requiring more than just analytical skills.

Method

Based on the collective experience of the authors, method development logically breaks into three interactive but independent activities pre-development, development and post-development. Each of these phases comprises a range of scientific inputs and outputs variously from pathologists, published literature and administration.

Results

	Phase	Requirements
Pre-developmental	**CLINICAL NEED** Prelude to every new method development Requests must be avidly pursued in a structured way so they do not falter early Laboratory responses must be expedient and sufficiently enthusiastic Requests can be initiated internally or by external enquiry	• Requires an established laboratory mechanism to respond to requests for new tests • Formation of a small development group of interested pathologists and scientists to maintain progress and dialogue • Survey of compatible laboratories offering the test and on what basis • Assessment of diagnostic importance • Extensive literature search of test utility, application and interpretation
	BUSINESS CASE Essential for administrative support and resource allocation Not necessarily a financial analysis but done with cost effectiveness in mind Needs to be consistent with laboratory strategic plan Possibly the most perplexing aspect for laboratory staff	• Circumspect analysis of the benefits accrued from provision of the test in terms of patient outcomes • Establish priorities with other scheduled laboratory commitments • Estimate of resources (equipment and staffing) and an estimate of developmental time
	FEASIBILITY STUDY Process to examine all the available test methods Essential prior to test commencement or development An in-depth assessment of the lab capability or otherwise	• Literature review of published applications • Determine availability of commercial test products • Decision for in-house vs commercial test methods • Consideration of equipment and reagents required
Development	**VERIFICATION** Verification is used when there is little or no further scientific input into the test Installation of a commercial test according to manufacturer's instructions Modification of an existing test for purposes of better performance, ease of use, speed, cost or platform change	• Ascertain test meets (or exceeds) performance criteria as declared by the manufacturer of a commercial product • Modifications without any substantial procedural change to an existing test requires only to show compatible (or improved) results against the existing procedure
	VALIDATION Design and development of entirely new test from first principles on a selected analytical platform Can be adapted from a published method or de-novo test construction Requires extensive knowledge of analyte properties Requires technological skills to control and manipulate instrumentation	• Derivation of optimised analytical conditions and instrument parameters, • Examine the test to meet the expected quality standards of accuracy, imprecision, linearity and interferences • Write a procedure with sufficient details to be replicated by an uninvolved scientist • Submit a validation report to a Quality Management group for scrutiny under regulatory guidelines
	SUITABILITY AND ROBUSTNESS Test method to be tested on the bench in a manner representing the demands of a routine environment Potential problems to be anticipated in advance of commissioning	• Test submitted to routine staff without express experience to the test • Difficult or confusing aspects to be rectified • Prove the ability of test to withstand the routine environment
Post-developmental	**QUALITY MANAGEMENT** Very familiar requirement to scientists Monitor the test output continuously in relation to the defined quality performance standards and define the acceptance/rejection criteria	• Create control charts inside the laboratory quality system • Participate in External Quality Assurance scheme if available • Otherwise engage in sample exchange with another independent laboratory
	COSTINGS AND STOCK CONTROL Establish the technical components contributing to test cost Usually does not include facility costs (e.g. building, power)	• Summarise all the consumable costs including reagents, calibrators, controls and disposables • Assess staff time on bench for average batch completion • Assess instrument maintenance costs and capital depreciation • Determine what stock must be held on hand to maintain uninterrupted service provision
	TRAINING AND COMPETENCIES Establish a training program for bench staff Define standards required for competency signoff allowing unsupervised operation	• Active bench training of staff and continual attention to their progression • Rapid follow-up to staff enquiries regarding the test • Inclusion of staff on competency register • Remain available to maintain test performance and provide remedial solutions to any problems
	DISTRIBUTIONS Alert potential requestors of test availability	• Write entry into the Lab Handbook describing all the features of the test including purpose, correct sample, TAT, reference limits and UOM • Write and take ownership of a comprehensive protocol to be held in Laboratory Documentation system and to be reviewed and updated according to expected schedule • Write description of the test in Lab Newsletter or similar promotional material • Present formal internal and external lectures to staff and requesters characterising the new test • Publish noteworthy methods in refereed local and international journals
	POST LAUNCH AUDIT Retrospective analysis of test performance	• Gain information regarding test request rates, requester locations, any complaints or suggestions, incorrect specimens etc • Reassess robustness in terms of average TAT, batch repeats, instrument failures and continuous improvements to the method • Audit appropriate use and interpretation by requestors • Publish novel clinical findings

Conclusion

Total process of method development requires the analyst to engage in a range of activities outside of the bench and to exercise a set of skills beyond analytical. The authors support training and continuing professional development in the total method development process as described.