

Letter to the Editor

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Total pathway to method validation

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To the Editor,

The role of the medical laboratory scientist (MLS) in method evaluation development and implementation 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. This is in keeping with the changing expectancies of the modern clinical laboratory [1] and the advancing role of MLSs within them. The current IFCC and EFLM education and training syllabus, reflects this [2, 3].

Here, we aim to create a roadmap for the total pathway to method validation to demonstrate the level of input required of MLSs to successfully validate their proposed method. The collective experience of the authors has shown that development pathways logically break into three interactive but independent activities namely pre-

development, development and post-development. Each of these phases comprises inputs and outputs variously from pathologists, scientists, clinicians, published literature, guidelines and administration (Table 1).

The pre-development phase starts with clinical assessment in terms of purpose and likely demand. Definition of the project and the purpose of the assay are paramount in advance of commencement. There must be a clear statement of intent which should be embodied within a formal protocol. Projects may falter at this point unless there is an assignment of responsibilities and a conviction by the group to proceed. Engagement with the relevant specialists is mandatory at this point and the dialogue must be bidirectional so that both perspectives are clearly defined. The drive forward can come from the specialties or from the laboratory itself, but afterwards the initiatives and momentum comes from MLS who are necessarily required to do the bulk of the work hereafter.

After the decision to proceed has been made the MLS needs to engage in an exhaustive literature review which mostly targets existing methodologies and the technical options. Part of this search will include a survey of other clinical laboratories that may be already active with the test. This helps to assure there is regional or global interest in the test as well as to provide potential collaborative support. Accessibility to an external quality assurance program is sought if one exists.

At this point, the MLS has assumed responsibility for either continuance or cessation of the project. This becomes dependent on a feasibility study to assess selection and suitability of available equipment. In essence, the MLS assesses the analytical requirements and determines whether the laboratory is capable of proceeding in terms of resources, instruments and anticipated development time. If the project is feasible continuation now requires a business case which covers, clinical need, technical matters in terms of reagents and instruments and various financial elements surrounding these. The intention is to convince administration of the worth of the project, assign resources, seek the various authorities and align with strategic planning and other priorities. The business case is not merely an accountancy exercise because final test cost is usually not the key determinant at this time and is calculated later.

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Table 1: Total pathway to method validation.

	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	<ul style="list-style-type: none"> – 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	<ul style="list-style-type: none"> – 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
Development	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	<ul style="list-style-type: none"> – 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
	Verification	
	Verification is used when there is little or no further scientific input into the test Installing a commercial test according to manufacturer's instructions Modifying an existing test for purposes of better performance, ease of use, speed, cost or platform change	<ul style="list-style-type: none"> – 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
Post-developmental	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	<ul style="list-style-type: none"> – Determination of optimized 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	<ul style="list-style-type: none"> – Test submitted to routine staff without express experience to the test – Rectify any difficult or confusing aspects – Prove the ability of test to withstand the routine environment – Re-examine performance characteristics outside of the research bench
	Quality management	
	Very familiar requirement to scientists Monitor the test output continuously in relation to	<ul style="list-style-type: none"> – Create control charts within the laboratory quality system

Table 1: (continued)

Phase	Requirements
the defined quality performance standards and define the acceptance/rejection criteria	<ul style="list-style-type: none"> – Determine acceptance limits and ensure they are fit for purpose for intended use – Participate in External Quality Assurance scheme if available – Otherwise engage in sample exchange with another independent laboratory
Costings and stock control Establish the staffing and technical components contributing to test cost Usually does not include facility costs (e.g. building, power)	<ul style="list-style-type: none"> – Summarize 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 programme for bench staff Define standards required for competency signoff allowing unsupervised operation	<ul style="list-style-type: none"> – Document a training programme followed by active bench training of staff under direct supervision – Remain attentive to staff progress with rapid follow-up to staff enquiries – Include trained staff on a competency register – Remain available to maintain test performance and provide remedial solutions to any problems
Distributions Alert potential requestors of test availability	<ul style="list-style-type: none"> – Write an 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 a description of the test in the lab newsletter or similar promotional material – Present formal internal and external lectures to staff and requesters characterizing the new test and how it should be used and interpreted – Publish noteworthy methods in refereed local or international journals
Post-launch audit Retrospective analysis of test performance	<ul style="list-style-type: none"> – 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 based on the test

Prior to the development phase, the decision to proceed has already been made in terms of starting point and likely success. The feasibility phase would have made the choice for a commercial product (if one existed) or to commit to development in-house. Dependent on this, verification or a full validation will be needed. Verification is always less demanding. Validation is required if a new method is to be designed from ground up based on scientific principles and technological skill. The validation process is the sole responsibility of the MLS. The analytical difficulty may vary between projects as well as the analytical skill invested. However, the net outcome must be a rigorous and exacting investigation that adheres to the strict criteria detailed in international guidelines [4, 5]. Usually, these will be from organizations such as Food and Drug Administration (FDA), Clinical and Laboratory Standards Institute (CLSI) or Committee for Medicinal Products for Human Use (CHMP) of European Medicines Agency.

After completion of the verification or validation, a full report needs to be issued by the MLS. This must detail everything that has been done with accompanying data. The report must be circulated to a formally appointed quality group consisting of scientists and pathologists who can gauge the quality of the analysis and the suitability of the test for service inclusion. This quality group must understand the analytical, technical and clinical principles of the test and have a vested interest in outcome.

After successful verification/validation, the MLS must pursue several other activities prior to submitting the test for service. Foremost is the implementation of control mechanisms consisting of internal QC charts, an external quality assurance programme, acceptance/rejection criteria, uncertainty principles, commutability, instrument operational records and a maintenance programme. If other regional labs are also offering the same test then attempts should be made to harmonize the results. If there are differences then requesters should be alerted to them. The MLS is required to calculate the cost which includes all reagents and consumables (calibrators, internal/external controls) staff time per batch, expected batch sizes, instrument devaluation and repair. These costs need to be known to allow billing. Lab-wide costs such as occupancy and power, administrative overlay, mark-ups and contingency are usually calculated outside of the actual test cost and applied by administration. The MLS must also arrange for inventory and procurement (suppliers, delivery times and instrument maintenance schedules) to prevent service interruption subsequent to test inclusion. This requires forward estimates of the likely demand. Documentation describing collection requirements, sample handling, storage conditions and instability needs to go to specimen

services. The MLS must write the bench method in a suitable format for staff to follow. The method document must then be stored in the laboratory documentation system for retrieval and future updates. Training of staff ensues with traceable competency assignments. An entry is written for the laboratory handbook to alert and advise potential requestors. It must contain all relevant material regarding patient preparation, test requirements, interpretation and reference intervals/decision limits (usually generated during validation). Hereafter, the MLS usually relinquishes some of the responsibilities to other relevant staff. All electronic online test lists and applications must be updated to reflect the changes. New test codes may need to be created within the Laboratory Information System (LIS). Page layout, report design, fixed and reflex comments, reference limits and units must be designed usually by the development group who best understand the test and its implications. The MLS will oversee a post-launch audit to monitor and record batch failures/causes, analytical/instrument problems, test robustness (ability to withstand variations from the SOP), turnaround time, request rates, abnormal result rates, utilization and enquiries/commentaries. If the method is substantively novel the MLS should endeavour to publish the work. Any interesting clinical findings and unique cases should also be reported in various formats such as colloquia, special interest groups and related journals.

In summary, it is not sufficient for the MLS to be solely adept at analysis. They need to have a thorough understanding of all facets of the process from conception to completion and this requires a much wider scope of involvement. The manifesto of laboratory medicine professionals clearly alludes to this [6]. The labscape is projecting further from just bench practice into stewardship and the provision of an entire diagnostic service. The generation of a numeric output is insufficient in itself. MLSs must be conversant with all the tests from their facility and especially those for which they are responsible or have designed themselves. Furthermore, MLSs need to be aware of their changing roles and of emerging technologies when selecting and optimizing their preferred methods or planning for future ones [7].

Finally, this total pathway requires the MLS to be proficient in their ability to conceive and direct validation processes starting with the opening strategy to gain clinical and administrative support before embarking on the test method itself. The methodology can be designed from ground up using scientific principles or implemented from commercial or published methods. It must be technically robust enough to be transferred into the routine environment and survive scrutiny from rigorous quality and

regulatory inspection. The MLS must then arrange for the adoption of the test into the laboratory service and ensure it is reliably and consistently applied. This includes proper usage and interpretation of the test for its intended purpose.

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