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ORIGINAL ARTICLE

Validation Protocol: First Step of a Lean-Total Quality Management Principle in a New Laboratory Set-up in a Tertiary Care Hospital in India

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Abstract Method validation is pursued as the first step in establishing Lean-Total Quality Management in a new clinical laboratory, in order to eliminate error in test results. Validation of all the new tests were done (with particular reference to alkaline phosphatase) by verifying reference intervals, analytical accuracy and precision, inter-assay and intra-assay variations, analytical sensitivity, limit of detection, linearity and reportable range, i.e. (i) Analytical measurement range (AMR) and (ii) Clinically reportable range (CRR). Our obtained reference range was within that of the manufacturer's and showed high degree of analytical accuracy between two laboratories ($r^2 = 0.99$). Precision was comparable with the manufacturer's claim with inter-assay variation CV 1.04% and intra-assay variation CV 1.54%. Lowest limit of detection was 1.0324 ± 0.007 with CV 0.34%. AMR was also verified with CV 1.26 and 0.69%, for level 1 and level 2 control sera, respectively. The assay was linear with different dilutions. Lean concept was also verified with high recovery percentage. Validation ensures that accurate and precise results are reported in a clinically relevant turn around time.

Keywords Validation · Total quality management · Alkaline phosphatase · Lean concept

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Introduction

There has been a continuous challenge in the health care system to provide better diagnosis, while maintaining standard quality credentials. Total Quality Management (TQM) include all divisions of the organization, namely, laboratory operations, information management, documents and record maintenance, materials and purchase, customer care, safety etc. Quality Management System requirements cover management's commitment to quality, its focus on customer, resource management, employee competence, process management, quality planning, design, review of incoming orders, purchasing, monitoring and measurement of its processes and products, calibration of measuring equipment, processes to resolve customer complaints, corrective/preventive actions and continuous quality improvement program [1].

During the initial phase of a laboratory set-up, product validation eliminates error in test results which is important from the view point of both patients, as well as of professional and regulatory bodies in the health care domain. With this in view, the present work has been carried out in a new Clinical Chemistry and Immunology laboratory set-up at Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, India.

According to FDA, validation is "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes" [2].

Laboratory Validation is a process that is employed to ensure that laboratory test data and results are consistent, accurate and precise [3]. The validation process for test methods, as well as the instrumentation that is used to perform the analysis, should have well-established system

of qualification phases: Installation qualification (IQ), Operational qualification (OQ) and Performance qualification (PQ) protocols [2, 4]. IQ establishes that the instrument is received as designed and that it is properly installed. OQ is carried out to ensure that the instrument is operating according to the defined specifications. PQ is supposed to ensure continued satisfactory performance of an instrument under actual running conditions during daily run. There are eleven main principles to the PQ laboratory test validation protocol. These are Specificity, Linearity, Accuracy, Precision, Robustness, Range, Limit of detection (LOD), Limit of quantitation (LOQ), Ruggedness, Selectivity, System, and Suitability.

Laboratory regulations require that performance for any new method be "verified" prior to reporting patient's test results. Precision and accuracy are specifically identified, along with analytical sensitivity, analytical specificity, reportable range, reference values, and any other applicable characteristic. The responsibility for method verification or validation resides with each laboratory. While manufacturers will often support to collect method validation data during the installation of new analytical systems, the laboratory is still accountable to see that adequate data has been collected and that this data shows that the new methods provide acceptable performance in the laboratory. Another motivation for this study was the fact that accreditation bodies, like College of American Pathologists (CAP) and National Accreditation Board for Testing and Calibration Laboratories, India (NABL) require that laboratories validate the performance of tests.

During the initial set-up phase of the laboratory, the entire loop of the testing process, including pre-analytical, analytical and post-analytical phases were designed. Complete evaluation of test performance must include precision, accuracy, linear range, detection limit, interferences, reference interval and reportable range [5, 6].

Lean is an effective business improvement methodology that is commonly used in manufacturing [7]. These principles have been applied to hospital services delivery and have been reported to be highly successful in the emergency department setting and the inpatient setting in case reports in peer reviewed journals [8, 9]. Therefore, these methods may have the potential to improve both the efficiency and quality of care delivery systems. Waste can be in many forms: time, motion, transportation, inefficient work flows, deficient supplies, re-work, handoffs, and process variation. Lean concept in health care delivery is "time-work flow" mapped and designed to remove the waste of health care delivery.

In this context, we have validated all the techniques and new tests by verifying reference intervals, analytical accuracy and precision, inter-assay and intra-assay variations, detection limit, linearity and reportable range. These are described in details in the following sections. Thus, TQM through validation and lean concept eliminates error in test results which is important for all. To the best of our knowledge, no such validation study from India has been published.

Materials and Methods

Samples were obtained from normal healthy adult volunteers or hospital outpatients after informed consent. In this work, we have taken alkaline phosphatase (ALP) processed during start-up phase of our new laboratory to enumerate all the validation steps discussed in this section. ALP was estimated by kinetic method based on the recommendations of the "International Federation for Clinical Chemistry" (IFCC) on the Olympus AU 400 auto analyzer (Olympus, Hamburg, Germany).

Following steps were taken to validate a new test:

Verification or Establishment of Reference Intervals

It is not required for a laboratory to establish its own reference limits, but satisfy that limits it uses are appropriate for the patients. According to CLSI document C 28-A2, it is very useful to be able to transfer a reference interval from one laboratory to another by some process of validation which is less costly and more convenient [10]. One can adopt reference limits from any of the following sources: manufacturer suggested, reference laboratory, published articles, neighboring laboratory or previous reference limits in the same laboratory.

In our laboratory, for checking reference intervals, we selected 20 representative healthy individuals, and the test was considered validated if, ≤ 2 of them were outside the manufacturer's proposed limit [10].

Verification of Analytic Accuracy

Agreement between test result and "true" result was done in mainly two ways: (i) comparison of results between new method and "reference" method (ii) Results using new method on certified reference materials (recovery). The first approach is most commonly used. For this we run 20 samples within testing range (CLSI document EP15-A2) by both new and comparative methods [11], and check whether the average bias between the two methods is within allowable limits or not.

In our case, establishing analytical accuracy involved testing 10 samples that span the entire range, by both the new (our laboratory) and the existing globally accredited laboratories' procedures, via linear regression analysis.

Verification of Precision

Precision implies repeatability, which means, analyze repeatedly to determine variation. To verify precision, abnormal samples were processed 3 times per run for 5 days, generating 15 replicates. This is called inter-assay variation.

For intra-assay variation, one abnormal sample was run 20 times.

Imprecision is quantified by calculating the mean, standard deviation (SD), and coefficient of variation (CV) of data collected from an analytical run:

$$CV = (SD \times 100)/\text{mean}.$$

Precision can be specified as: (i) repeatability (within run), (ii) intermediate precision (long term) and reproducibility (interlaboratory) [5].

Verification of Limit of Detection and Limit of Quantitation

LOD is the smallest amount that the method can detect to determine presence or absence of analyte [12]. LOQ is the smallest amount the method can measure quantitatively [12]. Conventionally LOD is defined as the lowest value that significantly exceeds the measurements of a blank sample [5].

This involves two steps: determination of values obtained with blank samples, and values obtained with low level positive samples. Blank samples often use the zero calibrator for an assay, while, low level positive samples were identified at or only slightly above the manufacturer's stated lowest detection limit.

CLSI document EP17-A describes the actual procedure [12], which is to run 20 blanks or low level samples; if <3 exceed stated blank value, one has to accept that value.

LOQ: The relative uncertainty of measurements at or just exceeding the LOD may be large, and often a quantitative result is not reported. LOQ constitutes the lowest limit of the reportable range for quantitative results of an assay [5].

Analytical Sensitivity

The term "analytical sensitivity" is sometimes used interchangeably with LOD or 'lower LOD' in many diagnostic laboratories. But here we will prefer to use 'LOD' due to its more precise definition and common use [12].

It is the ability of an analytical method to assess small variations of the concentration of analyte [13]. This is often expressed as the slope of the calibration curve [14]. The steeper the slope of the calibration curve, the assay is more sensitive. In reality, analytical sensitivity depends on the precision of the method.

Verification of Analytic Interferences

Most commonly, this involves listing stated interferences from manufacturer, and evaluating samples in correlation studies for differences (outliers), investigating causes of interference. It is often difficult to determine exact cause of interference, except for common causes, like, hemolysis, lipemia, icterus, related compounds, drugs, dietary substances, sample additives etc. [15].

The list is quite extensive. Therefore, we can use manufacturer defined potential interfering substances as our exclusion criteria for sample collection.

Verification of Reportable Range

Reportable range is the span of test result values over which the lab can establish or verify the accuracy of the measurement response.

Analytical Measurement Range (AMR)

Range of analyte values that a method can directly measure on the specimen, without any dilution, or other pretreatment, not part of the usual assay process.

AMR must be verified before a method is introduced, and checked at least every 6 months (and after recalibration or major maintenance) while in use.

AMR verification must include three levels—low, midpoint, high. One can use commercial linearity materials, proficiency testing (PT) samples or patient samples with known results, standards or calibrators. It can also be done by calibration verification, if three samples that span the measurement range are used. In absence of commercial materials, one will need to create one's own materials. High and low samples can be mixed to create a mid-point sample. If it is found to be higher than measurement limit, one can dilute with low level sample to create a level near limit. If the sample is stable, one can aliquot and freeze for future use.

Clinically Reportable Range (CRR)

It is the range of analyte values that are reported as a quantitative result, allowing for specimen dilution or other pretreatment used to extend the actual AMR.

CRR is a clinical decision by the laboratory director, and does not require experiments or re-validation; however, dilution or concentration protocols must be specified in methods. Finally, we verify the reportable range: (i) AMR includes three levels—low, midpoint and high, for which different levels of control sera are used. (ii) CRR is the range of values that can be reported with sample dilution.

Lean Concept

We planned for the lean concept in our laboratory [8]. It is summarized below under four heads:

(I) Workflow: (a) minimizing batching and waiting, and (b) removing manual data entry tasks.
(II) Transportation: (a) using Pneumatic Tube system more often, and (b) standardization of sample delivery times.
(III) Supplies: (a) stockroom standardization and (b) changes in supply replenishment method.
(IV) Performance monitoring: (a) employees measured on delivery time and productivity.

We validated our lean system by validating process flow at each step and comparing the recovery between pneumatic system and manual transport. To this end, we processed the 10 samples carried by health care assistants from phlebotomy (first floor) to the laboratory (seventh floor), i.e., manual transport, which took around 15–20 min time. Simultaneously, we processed another set of the same samples, transported via the pneumatic system, which took around 1–3 min of transportation time. Then recovery percentage was calculated between the two modes of transport.

Results

In the present work, we have taken ALP processed during start-up phase of our new laboratory to enumerate all the validation steps discussed in the methods section previously. The validation results are described sequentially below:

Verification of Reference Range

Our obtained reference range for ALP is 42.2–108.8 U/L, which was within the manufacturer's reference range (30–120 U/L) (Table 1).

Verification of Analytic Accuracy

Comparison of analytical accuracy between two laboratories gave, $y = 0.98x + 4.93$, with the correlation coefficient, $r^2 = 0.99$, establishing a high degree of linear correlation and validating our laboratory's procedures (Table 2; Fig. 1).

Verification of Precision

Verification of Inter-assay Variations

CLSI protocol (EP15-A2) suggests abnormal specimens to be run 3 times per run for 5 days, generating 15 replicates.

Table 1 Reference interval for ALP (U/L)

Serial No.	Value obtained (U/L)
Sample 1	75.8
Sample 2	55.5
Sample 3	56.4
Sample 4	105.8
Sample 5	92.6
Sample 6	73.1
Sample 7	99.8
Sample 8	74.1
Sample 9	59
Sample 10	90
Sample 11	96.4
Sample 12	61.8
Sample 13	67.5
Sample 14	82.6
Sample 15	56.9
Sample 16	69.9
Sample 17	83.6
Sample 18	68
Sample 19	91.8
Sample 20	49
MEAN	75.48
SD	16.6
Reference range obtained	42.2–108.8
Manufacturer's reference range	30–120

Table 2 Inter laboratory method comparison

	Our laboratory values (Kokilaben hosp.) (U/L)	Other laboratory values* (U/L)	Recovery (%)
Sample 1	57.3	60.7	105.9
Sample 2	51.4	54	105.1
Sample 3	62	63.2	101.9
Sample 4	123.2	125	101.5
Sample 5	85.9	90.3	105.1
Sample 6	121.2	122.7	101.2
Sample 7	72.1	78.9	109.4
Sample 8	96.3	100.4	104.3
Sample 9	85.8	91.2	106.3
Sample 10	74	78.3	105.8
Mean recovery percentage			104.65
SD			2.54
Recovery percentage range			104.65 ± 2.54
%CV			2.43

* Sample was sent to CAP and NABL accredited laboratory for inter laboratory Comparison

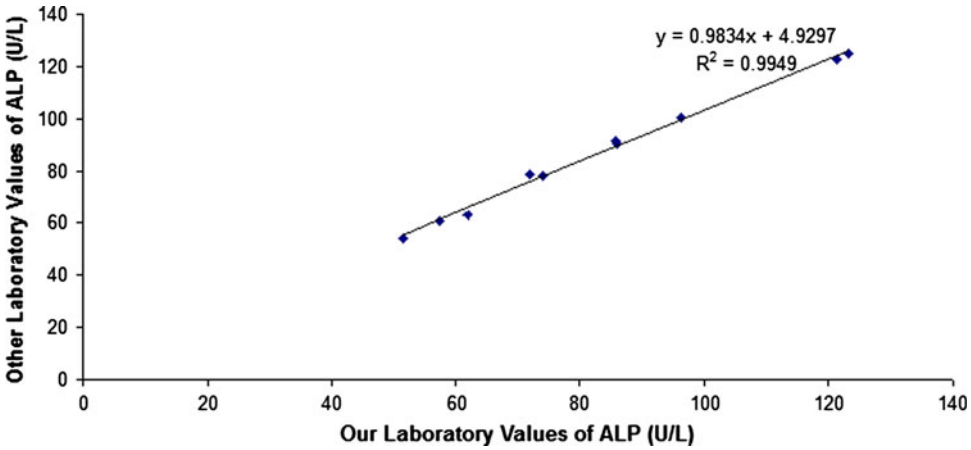

Fig. 1 Verification of analytical accuracy

We calculated SD and CV for the measurements and compared manufacturer's claim. If observed values found to be higher, one needs to evaluate the cause. Precision verification from 15 replicates gave a CV of 1.04%, comparable with the manufacturer's claim (Table 3).

Verification of Intra-assay Variations

Intra-assay variations were also within acceptable range (CV = 1.54%) (Table 4).

Verification of Limit of Detection and Limit of Quantitation

Verifying analytical sensitivity consisted of testing 20 blanks; which were accepted, if <3 exceed the stated blank value (Table 5). 20 blanks were all within the stated blank value, implying lower limit of detection.

Table 3 Verification of inter assay variations for ALP

Sample No.	Value obtained (U/L)
Run 1	
Sample 1	788.7
Sample 2	779.9
Sample 3	783
Run 2	
Sample 1	780.8
Sample 2	783.3
Sample 3	768.9
Run 3	
Sample 1	783.5
Sample 2	780.7
Sample 3	780
Run 4	
Sample 1	790
Sample 2	785.7
Sample 3	787.6
Run 5	
Sample 1	802.6
Sample 2	793.7
Sample 3	797.8
Mean	785.7
SD	8.2
%CV	1.04

Table 4 Verification of intra assay variations for ALP

Serial No.	Value obtained (U/L)
Sample 1	780.8
Sample 2	783.3
Sample 3	768.9
Sample 4	772.7
Sample 5	770.6
Sample 6	774.6
Sample 7	785
Sample 8	774
Sample 9	772
Sample 10	769.2
Sample 11	728.7
Sample 12	777.8
Sample 13	775.6
Sample 14	785.9
Sample 15	775.2
Sample 16	765.7
Sample 17	776.6
Sample 18	779.2
Sample 19	776.2
Sample 20	781.2
Mean	773.7
SD	11.90
%CV	1.54

Table 5 Verifying limit of detection

Blank readings (O.D.)	
Expected range:	0.00–1.2000
Serial No.	Observed readings (O.D.)
1	1.0236
2	1.0333
3	1.0342
4	1.0322
5	1.0325
6	1.0301
7	1.0332
8	1.0393
9	1.0317
10	1.0354
11	1.0339
12	1.0296
13	1.0310
14	1.0322
15	1.0320
16	1.0276
17	1.0388
18	1.0356
19	1.0301
20	1.0325
Mean	1.0324
SD	0.0035
Observed range	1.0324 ± 0.007
%CV	0.3416

Verification of AMR

AMR was verified as different levels of control sera were comparable with the manufacturer's claim, with CV 1.26 and 0.69%, for level 1 and level 2, respectively (Tables 6, 7).

Verification of Linearity and Recovery

For linearity check, we selected an abnormal sample above the linearity range, and progressively diluted it, until it crosses the lower limit of linearity.

The standardized test showed good linearity with different dilutions; recovery too was within an acceptable limit (90–110%), with $y = 0.99x - 2.81$ and $r^2 = 0.99$ between expected and observed values (Table 8; Figs. 2, 3).

Validation of Lean Concept, Pneumatic System

We validated our lean system by validating process flow at each step and comparing the recovery between the pneumatic system and manual transport. We processed the 10 samples carried by health care assistants from phlebotomy (first floor) to the laboratory (seventh floor), i.e., manual

Table 6 AMR verification with control serum level 1

Control serum level 1	ALP (U/L)
Manufacturer's range	83.9–140
Target value	112
Serial No.	Observed control serum level 1 range
1	103
2	104.4
3	101.4
4	104.1
5	101.9
6	103.4
7	104.6
8	101.7
9	105.1
10	102.7
Mean	103.2
SD	1.3
Observed range	103.2 ± 2.6
%CV	1.26

Table 7 AMR verification with control level 2

Control serum level 2	ALP (U/L)
Manufacturer's range	369–615
Target value	492
Serial No.	Observed control serum range
1	454.2
2	461.3
3	454.4
4	454.3
5	460.2
6	458.5
7	459.3
8	456.6
9	454.9
10	462.6
Mean	457.6
SD	3.16
Observed range	457.6 ± 6.32
%CV	0.69

Table 8 Linearity check and recovery for ALP

(Linearity range of ALP: 5–1000 U/L)				
Serial No.	Dilution	Observed value (U/L)	Expected value (U/L)	Recovery (%)
1	Undiluted	783.3	783.3	100
2	1:3 dilution	280.8	261.1	108
3	1:5 dilution	160	156.7	102
4	1:10 dilution	79.4	78.3	101
5	1:50 dilution	15.3	15.7	98
6	1:100 dilution	7.9	7.8	101
7	1:200 dilution	4.2	3.9	107
Mean recovery percentage				102.43
SD				3.69
Recovery percentage range				102.43 ± 7.38
% CV				3.6

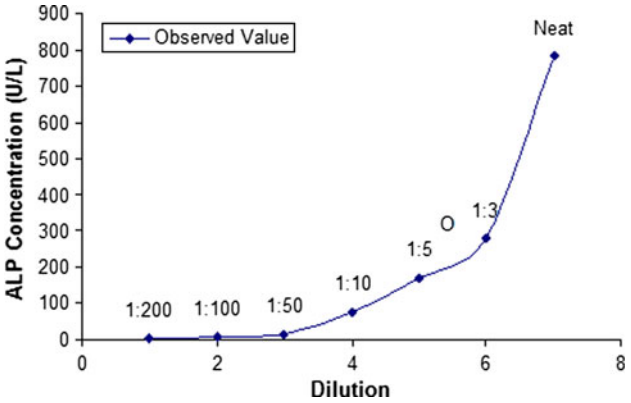

Fig. 2 Linearity check and recovery of ALP

transport, which took around 15 min of time. Simultaneously, we processed another set of the same samples sent by the pneumatic system, which took around 1–3 min of transportation time. Recovery averaged 100.89 ± 3.64 with $y = 1.03x - 1.70$ and $r^2 = 0.99$ (Table 9; Fig. 4).

Table 9 Comparison of ALP values between manual transport and pneumatic system

	ALP (U/L) (manual transport)	ALP (U/L) (pneumatic system)	Recovery (%)
Sample 1	71.6	72	100.6
Sample 2	75.2	76.3	101.5
Sample 3	223.8	228.9	102.3
Sample 4	77.2	78.5	101.7
Sample 5	99.4	100.1	100.7
Sample 6	78.2	77.3	98.8
Sample 7	78.1	77	98.6
Sample 8	75.5	78.9	104.5
Sample 9	60.9	61.7	101.3
Sample 10	80.4	79.5	98.9
Mean percentage recovery			100. 89
SD			1.82
Recovery percentage range			100.89 ± 3.64
% CV			1.8

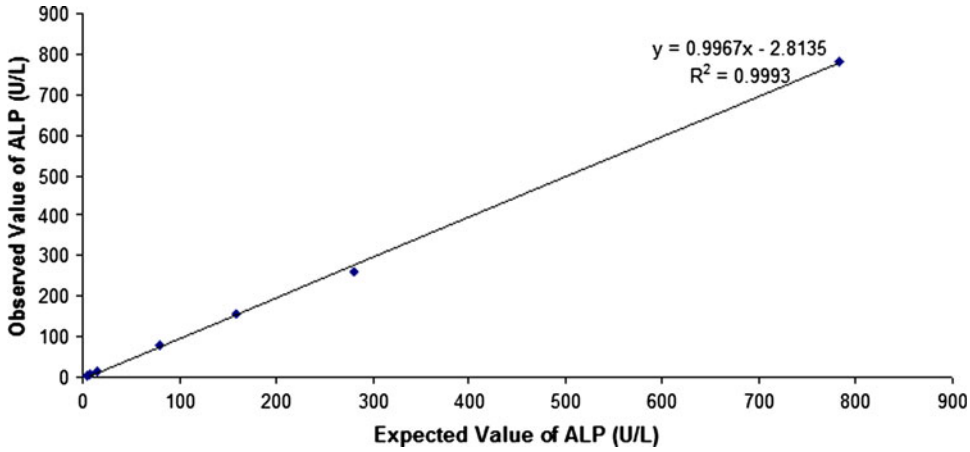

Fig. 3 Linearity check and recovery of ALP (linear regression analysis)

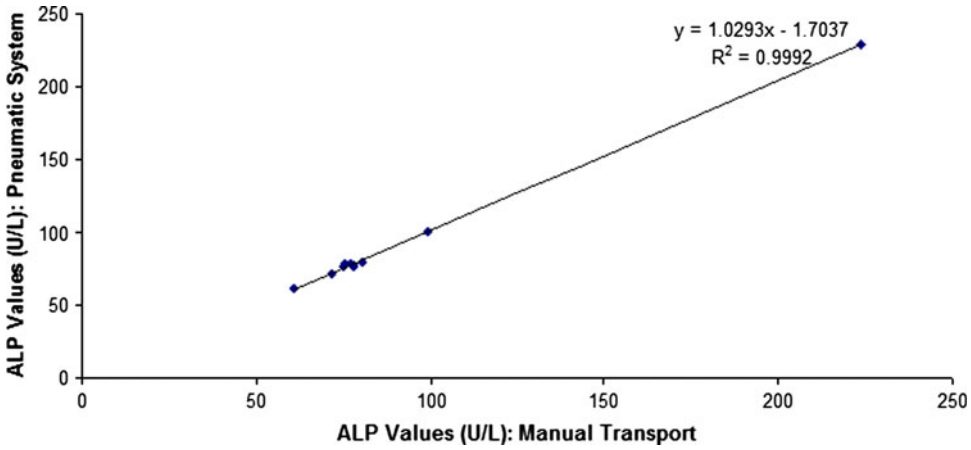

Fig. 4 Comparison between manual transport and lean transport

Discussion

In this work, we have validated all the techniques and new tests by verifying reference intervals, analytical accuracy and precision, inter-assay and intra-assay variations, limit of detection, linearity and reportable range.

We have used ALP processed during start-up phase of our laboratory to enumerate the above validation steps. Our obtained reference range for ALP was 42.2–108.8 U/L, which is within the manufacturer's reference range (30–120 U/L). Comparison of analytical accuracy between two laboratories gave, $y = 0.98x + 4.93$, with $r^2 = 0.99$, establishing a high degree of linear correlation and validating our laboratory procedures. Precision verification from 15 replicates (inter-assay variations) gave a coefficient of variation (CV) of 1.04%, comparable with the manufacturer's claim. Intra-assay variations were also within acceptable range (CV = 1.54%). 20 blanks were all within the stated blank value, implying detection limit.

AMR was verified too, as different levels of control sera were comparable with the manufacturer's claim, with CV = 1.26 and 0.69%, for level 1 and level 2 control sera, respectively. The standardized test showed good linearity with different dilutions; recovery too was within an acceptable limit (90–110%), with $y = 0.99x-2.81$ and $r^2 = 0.99$ between expected and observed values.

We validated our lean system by validating process flow at each step and comparing the recovery between the pneumatic system and manual transport. Lean concept was also verified with high recovery percentage (100.89 ± 3.64), with $y = 1.03x-1.70$ and $r^2 = 0.99$.

In today's era of a modern biochemical laboratory, a very important step with respect to the quality of the entire process is method validation. A laboratory physician checks the analytical result reports in order to verify that no error has occurred during their production [16]. Therefore, in this era of evidence-based medicine, the quality of evidence must be verified [17]. So, in the start up phase of any new laboratory, it is fundamental, to set up the evidence through validation of new process flow, new techniques and new test parameters.

Towards this goal, we have combined the Lean concept with TQM to make the work faster (using Lean principles) and better (using TQM principles). Validation and total quality management elements with close attention to the work flow of the laboratory ensure that accurate and precise results are reported in a clinically relevant turn around time. Thus, validation promotes an environment emphasizing patient safety and quality patient care.

Central to the role of any clinical laboratory is the desire to report accurate patient results. Validation of methods is an imperative part of that process. There are many occasions when practitioners use the concepts of validation methods such as establishing new tests, implementing commercial tests, or performing periodic assessment of established methods. Additionally, method validation is a requirement of laboratory regulations which state that performance of new methods be verified prior to reporting patient test results, and periodic assessment of accuracy and precision must occur. Despite the attention received of late in laboratory quality, and the new regulations and policies that have resulted there from, it remains an area that can be improved further. Many procedures of validation methods are still carried out inappropriately or are interpreted incorrectly. During laboratory accreditation process, the most frequently cited deficiency involves quality control problems.

Therefore through this work, we have done systematic validation of all the tests in the laboratory and thereby achieved a much better analysis and perfect reporting of test results. We have also designed report-formats and instituted written-down protocols to continuously monitor and ensure quality control, whenever a new procedure is adopted. This ensures a high reporting standard in all existing tests and new tests to be implemented in the future. This work thus constitutes a crucial step for long-term

quality patient care in the hospital. To the best of our knowledge, no such results have been reported in the literature, during the start-up phase of a new laboratory set-up in a tertiary care Hospital in India.

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