Original Article

Lot to Lot Reagent Verification: A Practical Guide on How to Do It?

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Abstract

Background: Lot to Lot reagent verification (LTLV) is done to check suitability of new lot of reagents for use. Except EP26, 2nd edition, 2022 by Clinical and Laboratory standards Institute, hardly any guidance document is available for LTLV. In present study, authors guide on how to perform LTLV using In-house & EP26 protocol with examples of Glucose, Aspartate Amino Transferase (AST) & Cholesterol using Quality control material and Patient Samples. The difficulties using EP26 protocol for LTLV have also been stated.

Methods: For In-house protocol,15 patient samples were assayed using current & candidate lot of reagents for Glucose, AST and Cholesterol. Acceptance Criteria were predetermined to verify the suitability of candidate lot. MedCalc software, current version 23 was used for statistical calculations. For EP26 protocol, in stage1, Total Allowable Error (TEa), Critical difference, Sr (within-run imprecision) & S_{WRL} (within reagent imprecision) & Statistical power of 0.8 were determined. In stage 2, number of patient samples needed to be assayed for LTLV was determined using Appendix A in EP26 & Rejection Limit (RL) was derived. Absolute Mean Difference was calculated and verified to be less than RL.

Results: For In house protocol, all the predetermined Acceptance criteria were met by the candidate lot of reagents. For EP26 protocol, Absolute Mean difference between the results obtained in current and candidate lot was less than the determined RL.

Conclusion: Laboratories Can use Inhouse protocol or EP26 protocol with its inherent difficulties to perform LTLV using guidance provided in this article.

Keywords: lot; reagent; verification; EP26; In-house; protocol

Introduction

Laboratory tests are used for screening & diagnosing a disease, monitoring treatment or for prognosis.[1] For the purpose of monitoring & prognosticating a disease, the laboratories should maintain consistency of results. Verification of new lot of reagents for its suitability for use is a good laboratory practice and is a requirement to be met as per International & National Standards. [2, 3] Reagents lot verification practices vary widely among laboratories with regards to the number of samples evaluated, the type of material tested, and the criteria used for acceptance.[4] Challenges faced with Lot-To-Lot reagent Verification (LTLV) include: Definition of a reagent lot, Selecting acceptance target, Commutability of material used, Range of concentration and number of samples used, Experimental design and statistical analysis to be done.[5] Laboratories use either In-house protocol or EP26: User Evaluation of Acceptability of a Reagent Lot change, 2nd edition, 2022[6] as a guidance document to verify the consistency of results between consecutive reagent lot changes. Our study provides a guide

to implement reagent lot to lot verification with examples for Glucose, Aspartate Amino Transferase (AST) & Cholesterol using patient samples & Quality Control Material by In-house protocol and EP 26 protocol[6]. The current article also discusses the difficulties observed while using EP26 protocol for LTLV in our study.

Materials and Methods

In the current study for Lot-To-Lot Reagent verification (LTLV), two protocols (In-house & EP 26) were used. Assays were carried for Glucose, AST & Cholesterol concurrently on receipt of new lot of lot reagents (candidate lot) & before the old lot (current lot) of reagents got exhausted. Patient samples as well as Internal Quality Control (IQC) material (Bio-Rad) Control Level 1 (Lot No. 89731) and Level 2 (Lot no. 89712) were used in the study. All the above assays were performed in Fully Automated Chemistry Analyser Mispa Nano Plus, Agappe diagnostics.

In-house protocol

Patient's samples were chosen to avoid the issue of commutability seen in IQC material for In-house Protocol. Patient samples for Glucose, AST and Cholesterol were chosen at three concentrations. Guidance in selecting concentration for patient samples in current study was derived from Medical Decision Levels chart provided in Westgard QC [7] and also to span the Analytical Measuring Range (AMR) of the method. A total of 15 patient samples (5 each at three concentrations) were assayed using current & candidate lot of reagents for Glucose, AST and Cholesterol. Mean difference % (Delta difference in %) between the results obtained in both lots were calculated & other calculations were done to meet In-house acceptance criteria as described below.

Acceptance for lot verification for in-house protocol

Acceptance for lot verification for In-house protocol were as followed: - Average delta % (Mean difference) in results obtained in patient's sample results between two lots be <10%. Delta % = (candidate lot result – current lot result / current lot result x 100). Passing- Bablok regression analysis was done by MedCalc software version 23 with the acceptance criteria being Regression line gradient between 0.9 and 1.1. R2 >0.95. Mean difference % between the results obtained between two lots <1/3 of Total Allowable Error (TEa). For choosing the TEa, Westgard website was consulted.[8] (In case if this criterion is not met than Total TEa rather than 1/3 of TEa was considered as per the Mc Master University Protocol) [9]. Paired t -test between the current and candidate lots of reagent – Average relative difference significantly different from zero (alpha is set at 0.005)

EP 26 (User evaluation of acceptability of a reagent lot change, 2nd edition, 2022) protocol using two stages

To use EP 26 document, Bio rad Level 1 & Level 2 IQC material were assayed 20 times in a single run in current lot & candidate lot to calculate Sr (SD obtained for a sample within a single run) & S_{WRL} (SD obtained from 20 readings in different runs).

Stage 1: Protocol parameters determined as below

A relevant TEa was established for Glucose, AST and Cholesterol as 10%, 20% and 10% respectively using Westgard.[8] Critical difference was taken as half of TEa [10]. Sr (within-run imprecision) and S_{WRL} (within-reagent imprecision) values were obtained from IQC data at two decision levels of control material from historic IQC data of laboratory from current lot of reagents. Statistical power was chosen as 0.8 for Glucose, AST and Cholesterol tests. As per Kim et al[10] Rejection Limit (RL) was taken as 0.6x CD as this RL has 90% probability to detect variation in performance of new lot. EP 26 states that 0.70 X CD results in a statistical power close to 0.90, however when we use 0.6xCD the statistical power of RL around 0.9 is achieved for detecting clinically significant change while minimizing the probability of false rejection. Tables A1 to A3 from Appendix A of EP26 were then used to determine how many patient samples need to be tested to detect a reagent lot-to-lot difference that exceeds the CD. CD/S_{WRL} and Sr/S_{WRL} were calculated and used to select patient sample number to be tested for LTLV from tables A1 to A3 given in EP26.

Stage 2: Routine evaluation of candidate reagent lots

Mean Difference (MD) as Absolute difference between the results obtained using patient samples in lots Reagents were calculated. If the mean difference was less than Rejection limit (|MD| <RL), the candidate lot reagent was accepted for

routine use. If mean difference was more than RL, a Root Cause Analysis was done to identify the Root Cause and initiated corrective action using troubleshooting guidance provided by Thompson & Chester D.[11]

Results

Five different patient samples at three different concentrations were assayed in current & candidate lots of reagents for Glucose, AST & Cholesterol. The Mean difference % between them was then calculated. The results of this exercise are shown in Table No 1.

Table 1: Results of five patient samples assayed at three concentrations for glucose, AST, and cholesterol.

Patient	Concentration 1		Concentration 2		Concentration 3	
No.	Current lot	Candidate lot	Current lot	Candidate lot	Current lot	Candidate lot
Glucose						
	(57 mg/dl)		(114 mg/dl)		(311 mg/dl)	
1	58	59	113	116	311	313
2	57	58	116	114	310	312
3	59	59	115	114	314	311
4	58	57	114	113	312	313
5	56	57	113	115	311	314
Avg. Conc.	57.6	58.0	114.2	114.4	311.6	312.6
Mean Diff %	−0.69%		−0.18%		−0.32%	
AST						
	(22 U/L)		(35 U/L)		(142 IU)	
1	22	24	36	35	141	142
2	24	23	35	36	145	146
3	23	21	35	36	142	140
4	22	24	34	35	143	145
5	23	22	36	37	143	145
Avg. Conc.	22.8	22.8	35.2	35.8	142.8	143.6
Mean Diff %	0.00%		−1.70%		−0.56%	
Cholesterol						
	(103 mg/dl)		(184 mg/dl)		(245 mg/dl)	
1	103	104	184	182	246	247
2	105	103	185	183	244	245
3	102	104	183	182	247	247
4	104	103	184	185	246	244
5	103	105	185	184	245	246
Avg. Conc.	103.4	103.8	184.2	183.2	245.6	245.8
Mean Diff %	−0.39%		0.54%		−0.08%	

Once the results of Comparison studies were obtained using patient samples in current & candidate lots of reagents, predetermined acceptance criteria for our In-house protocol were used & the findings are depicted in Table 2.

Discussion

Laboratories play a vital role in treatment decision by providing accurate, precise, and consistent results. Consistency in result reporting is of most importance in sequential test results when critical decisions have to be made on any change in treatment modalities. Limited guidance is available on lot-to-lot verification of reagent change.[5, 6, 11, 12, 13] Clinical laboratories use either In-house protocol based on references like B.M. Katzman et al[4], A.C. Don-Wauchope[9], Kim et al[10], Thompson S & Chesher D[11] & Martindale et al [13]or use EP26[6]. Critical issues to be considered while performing LTLV verifications are, Type, number of samples & concentration levels to be used and Acceptance criteria to decide whether the new lot is acceptable or not. As regards number of patient sample and concentrations of samples to be tested for LTLV, published studies have used 1 to 20 samples using either Medical Decision Level concentration or Analytical Measuring Range to achieve a statistical power of 0.8 or 0.9.[4, 9, 11, 14] EP26 recommends a minimum of 3 patient's samples always to be tested for LTLV which may be dispersed among the target concentrations. In our study, we have used 5 patient samples at three different concentrations spanning the AMR. Kim et al[10] have concluded that >1/2 of

Table 2: Reagent lot verification and acceptability using in-house lot to lot verification protocol and predetermined acceptance criteria based on results shown in table 1.

In house acceptance criteria	Glucose Patient sample			AST Patient sample			Cholesterol patient sample		
Concentration of samples assayed	57 mg/dl	114 mg/dl	311 mg/dl	22 U/L	35 U/L	142 IU	103 mg/dl	184 mg/dl	245 mg/dl
Mean Difference (Average Delta) % <10%	0.69%	0.18%	0.32%	0%	1.7%	0.56%	0.39%	0.54%	0.08%
All value below < 10%		All value below < 10%			All value below < 10%			All value below < 10%	
Result		Acceptable			Acceptable			Acceptable	
Mean Difference (average delta) %<1/3 of TEa	0.69%	0.18%	0.32%	0%	1.7%	0.56%	0.39%	0.54%	0.08%
All value below 1/3 TEa i.e 3.33%		All value below 1/3 TEa i.e 3.33%			All value below 1/3 TEa i.e 6.66%			All value below 1/3 TEa i.e 3.33%	
(TEa 10%, 1/3 TEa=3.33%)		(TEa 10%, 1/3 TEa=3.33%)			(TEa 20%, 1/3 TEa=6.66%)			(TEa 10%, 1/3 TEa=3.33%)	
Result		Acceptable			Acceptable			Acceptable	
Paired T test P value (Two-tailed probability)	0.3739	0.8466	0.3943	0.6483	0.1419	0.7489	1	0.2080	0.3375
Which is > 0.05		Which is > 0.05			Which is > 0.05			Which is > 0.05	
Result		Acceptable			Acceptable			Acceptable	
(Coefficient of determination) >0.95		0.9999			0.995			0.9997	
Result		Acceptable			Acceptable			Acceptable	
Regressing line gradient (Slope)		1			1			1	
Result		Acceptable			Acceptable			Acceptable	

chemistry tests reagent lot to lot difference could be evaluated using only one patient sample. Our In-house protocol for LTLV uses 5 patient samples at three different concentrations & this 5-patient sample number also meets the number of samples required to be assayed as per tables given in appendix A of EP26 based on CD/S_{WRL} and Sr/S_{WRL}. Beside patient samples, IQC material can also be used for LTLV however commutability issues limit its use for this purpose[11]. Cho et al [15] have provided evidence that usefulness of the IQC material data in establishing the suitability of a new lot of reagents is limited. Studies published on acceptance criteria for In-house protocol for LTLV using either patient samples or QC material vary and are summarized below in Table no.3.

Laboratories can decide upon which and how many parameters will be used in their acceptance criteria for LTLV from the Table no.3 and it will depend upon availability of statistical software and expertise with the laboratory. If laboratory choses to use EP26 protocol then clinically relevant Allowable total Error (TEa), Critical Difference (CD), Statistical power & Rejection Limit have to be selected in stage 1 (Determining protocol parameters)[6]. TEa are established based on hierarchy models viz Model 1 (Clinical outcomes), Model 2 (Biological variation) and Model 3 (state of the art) as per Milan criteria [16]. For practical purposes, laboratories can use Westgard website[8] or European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) database[17] to select the TEa.

Critical difference (CD) represents the maximum lot to lot difference at which a candidate lot is acceptable for use without affecting clinical decision making. Unfortunately, EP26 does not provide a definite approach to determine CD and the onus is on the laboratory to determine the CD. Kim et al[10] have provided three options for determining CD 1)Reference change value (RCV) = CD ($1.96 \times 2^{0.5} \times (S^2_{WRL} + CVi^2)^{0.5}$, S_{WRL} is EP26 term for within reagent lot imprecision (intra assay imprecision) and CVi is within Subject biological variation. S_{WRL} is obtained from the historic IQC data available with the laboratory. Alternatively, S_{WRL} value can also be obtained from Manufacturer's Instructions for Use (IFU) stated usually as Interassay Imprecision. CVi data can be obtained from (EFLM) database [17] or from the Westgard website[18]. If no CVi data is available on either of the above resources then CVi can be considered as 10.0 % 2) CD = ½ of TEa. If TEa data is not available for particular analyte in either EFLM database or Westgard website then CD can be set as 10.0%. 3) CD can be based on Analytical Performance Specifications (APS) provided by External Quality Assessment (EQA) agencies. Kim et al[10] recommends to use stricter acceptable criteria either from Clinical Laboratory Improvement Amendments (CLIA) or Rili-BAEK as CD. When there are no defined acceptable limits for APS in either of the above EQA agencies then CD can be taken as 10% B.K. Katzman et[4] al have calculated CD based on Target performance goal and Target concentration as CD= Target performance goal x Target concentration. Tao et al [19] considers CD as CD=4.36 x CVWRL. Out of the above all the approaches for calculating CD, best option would be CD=1/2 of TEa because it avoids complicated calculations and is easy for determining CD. B.M. Katzman et [4]al sets statistical power 0.80 while using EP26. In our study we have chosen statistical power of 0.8 for using EP26. Kim et al [10]have inferred that rejection limit of 0.6 x CD can detect reagent lot-to-lot difference with ≥ 90%.

In our study we have used this recommendation to calculate RL which gives a chance to detect variability in the candidate lot reagents performance. After Stage 1, to use EP 26 Protocol, information derived from stage 1 is used to determine concentration(s) of patient samples to be tested, number of samples to be evaluated at each concentration & then RL is used to evaluate the average difference observed at each concentration. To determine the number of samples to be assayed in current & candidate lot, laboratory has to use Table A1 to A3 provided in Appendix A of EP26. For this purpose, laboratory need values of CD/S_{WRL} and Sr/S_{WRL}.

Table 3: Acceptance criteria used by various studies for LTLV either using patient samples and/or IQC material.

Material used for LTLV	Cho et al[15]	Thompson S & Chesher D[11]	A.C. Don-Wauchope[9]	B.M. Katzman et al[4]
Patient's sample	Delta % of the patient's sample results obtained with the new and old lots fall within ± 10%	In paired t-test between the two lots – Is the Average relative difference significantly different from zero (alpha is set at 0.05)?	Difference between results in new & old lot of reagents should be one third of Total Error Allowable (TE_a) for a particular analyte	<10% mean difference between reagent lots
		A comparison based on biological variation – Is the difference between the two sets of results <33% of the within-subject biological variation (CV_i)?	-	Intercept (<50% Lowest reportable concentration)
		Based on Royal College of Pathologists of Australasia Quality Assurance Programs (RC-QAP)	Slope of regression line between 0.9 & 1.1	Slope between 0.90 and 1.10
		Do any of the individual differences exceed these specifications?	Linear regression equation should fall within 10% of equivalence	
				$R^2 > 0.95$
IQC material	New lot of reagents acceptable when the results tested with new lots fall into mean ± 2SD derived from the initial evaluation study	NA	Results using QC material with new lot of reagents should fall within 2 standard deviations of the current mean	NA

Approaches to determine CD have been discussed earlier. Sr & S$_{WRL}$ values can be obtained from laboratory's historic IQC data & performance verification data for the current lot of reagents. To obtain S$_{WRL}$ value from candidate lot, laboratory has to capture new 20 QC events which makes S$_{WRL}$ from candidate lot impracticable for routine use, so we recommend to use Sr & S$_{WRL}$ values from IQC data of control material at two decision levels from current lot of reagents. Manufactures IFU also provide values for Sr and S$_{WRL}$, The Sr and S$_{WRL}$ values provided by the manufacturer are derived in highly regulated conditions which may not reflect the infield/real life situation of laboratories, so we recommend to use Sr and S$_{WRL}$ values from laboratory's historic IQC data of control material assayed at two decision levels in both lots of reagents.

In our study as we have used five sets of patient samples at each of the three concentrations, we chose Table A3 to determine the number of patients samples to be assayed in current candidate lots.

Table 4: Parameter used in our study to determine number of patient samples to be assayed for LTLV using table A3 of appendix A in EP26.

Parameter	Decision Levels	Sr	S$_{WRL}$	TEa	CD=1/2 TEa	CD/ S$_{WRL}$	Sr/ S$_{WRL}$	RL	Number of samples to be tested as per Table A3 of Appendix A of EP26
Glucose	Level 1	1.22	1.87	10	5	3.21	0.65	3	5
	level 2	2.59	5.8	10	5	1.03	0.45	3	5
Cholesterol	Level 1	2.42	2.9	10	5	2.07	0.83	3	3
	level 2	3.64	5.88	10	5	1.02	0.62	3	3
AST	Level 1	1.35	2.65	20	10	4.53	0.51	6	5
	level 2	2.23	4.54	20	10	2.64	0.49	6	5

Lastly Rejection Limit is calculated & it is used to see that Absolute Mean Difference between the results obtained between current & candidate lot of reagents is less than RL. (|MD| <RL), Difficulties observed by us and other researchers [4, 9, 10, 11, 20] while using EP26A/EP26 are summarized below: RL is decided by CD which largely depends on TEa and

Table 5: Simplified steps to use EP 26 Protocol using worked examples of Glucose, AST & Cholesterol reagents (adapted from Supplementary material in study by Kim et al[10]).

Evaluation Steps	Decision Level 1	Decision Level 2
Glucose		
Step 1: Parameters (S_r, S_{WRL})	S_r 1.22% S_{WRL}: 1.87%	S_r 2.59% S_{WRL}: 5.8%
Step 2: Critical Difference (CD)	CD using TEa=10, CD=5	CD using TEa=10, CD=5
Step 3: Ratios (CD/S_{WRL}, S_r/S_{WRL})	CD/S_{WRL} = 3.21, S_r/S_{WRL} = 0.65	CD/S_{WRL} = 1.03, S_r/S_{WRL} = 0.45
Step 4: Sample Size & RL	Power: 0.8, Size: 5, RL: 3 (0.6xCD)	Power: 0.8, Size: 5, RL: 3 (0.6xCD)
Step 5: Assay Results (mg/dl)	Current/Cand: 57.6/58	Current/Cand: 311.6/312.6
Step 6: |MD| < RL	MD: 0.4, RL: 3	MD: 1, RL: 3
Result	**Acceptable**	**Acceptable**
AST		
Step 1: Parameters (S_r, S_{WRL})	S_r 1.35% S_{WRL}: 2.65%	S_r: 2.23% S_{WRL}: 4.54%
Step 2: Critical Difference (CD)	CD using TEa=20, CD=10	CD using TEa=20, CD=10
Step 3: Ratios (CD/S_{WRL}, S_r/S_{WRL})	CD/S_{WRL} = 4.53, S_r/S_{WRL} = 0.51	CD/S_{WRL} = 2.64, S_r/S_{WRL} = 0.49
Step 4: Sample Size & RL	Power: 0.8, Size: 5, RL: 6 (0.6xCD)	Power: 0.8, Size: 5, RL: 6 (0.6xCD)
Step 5: Assay Results (U/L)	Current/Cand: 35.2/35.8	Current/Cand: 142.8/143.6
Step 6: |MD| < RL	MD: 0.6, RL: 6	MD: 0.8, RL: 6
Result	**Acceptable**	**Acceptable**
Cholesterol		
Step 1: Parameters (S_r, S_{WRL})	S_r 2.42% S_{WRL}: 2.9%	S_r 3.64% S_{WRL}: 5.88%
Step 2: Critical Difference (CD)	CD using TEa=10, CD=5	CD using TEa=10, CD=5
Step 3: Ratios (CD/S_{WRL}, S_r/S_{WRL})	CD/S_{WRL} = 2.07, S_r/S_{WRL} = 0.83	CD/S_{WRL} = 1.02, S_r/S_{WRL} = 0.62
Step 4: Sample Size & RL	Power: 0.8, Size: 3, RL: 3 (0.6xCD)	Power: 0.8, Size: 3, RL: 3 (0.6xCD)
Step 5: Assay Results (mg/dl)	Current/Cand: 103.4/103.8	Current/Cand: 245.6/245.8
Step 6: |MD| < RL	MD: 0.4, RL: 3	MD: 0.2, RL: 3
Result	**Acceptable**	**Acceptable**

Note: Manufacturer's IFU for S_r and S_{WRL} was not used; however, laboratories have the option to use it for detecting S_r and S_{WRL}.

which TEa to be used is not clearly stated in EP26. Samples sizes and RL vary on the approaches to determine CD viz RCV, TEa or EQA/PT. EP26 often suggests large sample size making this protocol at times impractical to be used in terms of technologist's time needed, cost of reagents used, availability of instrument time for LTLV and inaccessibility to the required number of patient samples. Columns in tables A1 to A3 in Appendix A of EP26 at times do not match the CD/S_{WRL} & Sr/S_{WRL} decided by the laboratory, raising difficulties to decide upon the patient samples for LTLV. EP26 is not designed to monitor the long-term trends of lot-to-lot performance.

Conclusion

If change in performance of recent lots is not adequately verified statistically, it may affect the quality of the results offered by the laboratory. Different protocols for LTLV are available in literature and laboratory has to take a pragmatic approach in selecting protocols for its own LTLV. EP26 provides guidance on LTLV, however it leaves acceptance criteria for LTLV to be determined by the laboratory, therefore harmonization of acceptance criteria for LTLV is needed. In our study, we have found EP26 protocol to be quite demanding in terms of cost, expertise needed, instrument time and type and number of patient samples needed for LTLV. A small sized laboratory with its limited resources can design its own In-house protocol which provides enough statistical robustness to perform LTLV using guidance provided in this article.

Ethical Clearance

The study used residual patient samples after reporting their results, patients were not harmed during the study and no patient's identity is disclosed in the study so as per Helsinki declaration, the ethical clearance is waived.

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Abbreviations: None.

Competing Interests: Biochemistry, Histopathology, Cytology and Immunology.

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