

The Use of Analytical Method Validation to Compare Results Obtained Using Boreal Laser HF Analyse and Isokinetic Sampling Technique

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Abstract

Laboratories have a professional obligation to provide accurate and reliable analytical results to customers. The Laboratory should justify the customer's trust by providing the correct answer to the analytical part of the problem, in other words, results that have demonstrable 'fitness for purpose'. Analytical method validation is one of the measures universally recognised by laboratories as a necessity for a comprehensive system of quality assurance.

Reliable analytical results are required for compliance with international regulations in almost all areas of analysis. Method validation is an essential component of the measures that laboratories should employ to ensure that they produce accurate and reliable results, hence ensuring business continuity.

International organizations like ISO, AOAC AND IUPAC have published guidelines for method validation techniques. It is important that laboratories should adopt these guidelines and incorporate them into their method validation procedures. Method validation should, if possible, have means of involving the customers that will be using the results. The involvement of customers ensures that method performance, as required by customers, is incorporated early before a method is developed.

This paper discusses in details the conceptual aspects of method validation and its management, method validation processes, highlights method validation key performance characteristics and discusses method validation schemes. It uses as an example, statistical method validation techniques to establish if there is any significant (0.05) difference between gaseous fluoride results, from Mozal pot rooms roofvent, obtained using Boreal Laser HF analyser and Isokinetic Sampling techniques (ISO 9096).

The results indicate that there is no significant (0.05) difference between HF Results obtained using the two methods.

1 INTRODUCTION

Reliable analytical results are required for compliance with international regulations in almost all areas analysis. Analytical method validation is one of the measure universally recognise by laboratories as a necessity for a comprehensive system of quality assurance. Method validation is an essential component of the measure that laboratories should employ to ensure that they produce accurate and reliable results hence, ensuring business continuity.

International organizations like ISO, ILAC, AOAC and UPAC have published guidelines for method validation techniques. It is important that laboratory adopt these guidelines and incorporate them into their method validation procedures. Method validation should, if possible, have means of involving the customers that will be using the results. The involvement of customers ensures that method performance, as required by customers, is incorporated early before a method is developed.

Methods can be validation using different techniques^{1, 2, 3, 4, 4, 5}. Each author discusses the importance of the need to demonstrate the accuracy and reliability of the methods for a particular analysis. The statistical requirements for method validation a are discussed by different author. Van Heyden *at al.* covers aspects related to ruggedness and robustness of a method⁷, uncertainties of measurement are well covered by^{3, 6, 8}, the evaluation of linearity is discusses in ^{3, 9, 10}, and Mark; trullols *et aland* Valcarcel *et al.* discuss the importance of validating qualitative method^{11, 12, 13} whereas Ye *at al.* visits the design of experimental data requirement for method validation¹⁴. Mcdowall looks at how laboratory information management system (LIMS) could be used in method validation and he proposed way forward toward integration⁴.

1.1 Responsibility Of Carrying Validation And Verification

Laboratories have a professional obligation to provide analytical results to customers. The analytical results provided should be appropriate to solve intended problem(s). Eurachem stated that “the laboratory and its staff have a clear responsibility to justify the customer’s trust by providing the right answer to the analytical part of the problem, in other words results that have demonstrable ‘fitness for purpose’³. This means that , it is a duty of the laboratory to ensure that analytical results provided are accurate and reliable. To achieve the required reliability, the laboratory employs quality assurance, quality control and analytical method validation systems.

When a laboratory is to start using a new method, it is the responsibility of the laboratory to check and verify that it has enough competencies to use the method². Competency in this context means overall competency that covers instrumentation, intellectual capital, reagents, the analytical methodology, calibration standards and certified reference materials to run the method.

The laboratory has to determine whether to use an already existing method from organisation or institutions such as ASTM, SABS, EPA, ISO, IUPAC, etc or to develop a new method. In most cases,. In whichever case, the method will have to be validated for is suitability in that particular laboratory. Wood highlighted that “the extent of laboratory internal validation and verification depends on the context in which the method is to be used”². Hence some

methods will require rigor validation whilst other might go through partial validation. Customer's requirement will determine the extent of validation required

1.2 Deciding the Degree of Validation Required

The laboratory has to decide and distinguish the method performance parameters that need to be validated. Characterization of method performance is an expensive process and inevitably it may be constrained by personnel requirement, time and cost considerations. Starting with a carefully considered analytical specification provides a good base on which to plan the validation process.

When deciding the degree of validation required, the laboratory should taking into account customer's requirements, existing personnel and the need for compatibility with other similar methods already in use within the laboratory or used by other laboratories.

Laboratories should remember that striking the balance between time and costs constraints and the need to validate the method is difficult and in some circumstances it may be more appropriate to subcontract the work to another laboratory where it can be performed on a routine basis.

1.2.1 Laboratory Competency Requirements

The identification of a need to introduce a new analytical method often requires the laboratory to have enough competencies to develop validate and apply the method. The level of skills required depends on the analytical method to be developed, the level of accuracy and precision required. Eurachem emphasizes that "the operator carrying out the studied must be competent in the field of work understudy and have sufficient knowledge related to the work to be able to make appropriate decision from observation made as the study progresses"³.

Laboratory competency is a key requirement in development of new analytical method. In a case where a laboratory lacks the competency, the laboratory might be forced to hire new people with special skills and expertise and, procure equipment and laboratory consumables suitable for the method. Otherwise, the laboratory would be compelled to outsource the analysis from competent counterparts.

The characteristics of the method determine whichever way to go. Method characteristics can be divided into three categories.

Application characteristics are factors that determine whether a method can be implemented in a particular laboratory situation. They consist of cost-per-test, species to be analysed, sample size, turnaround time, workload, equipment and personnel requirements, space, regulatory requirement, health, safety and environmental considerations.

Methodology characteristics are factors, which in principle, should contribute to best performance. In general, these are concerned with the analytical quality control, sensitivity and specificity of the method. They include reference material, optimisation of test conditions, principles of standardisation ad etc.

Performance characteristics are factors, which, in practice, demonstrate how well a method performs. These include precision, recovery, interference, accuracy, detection limit, limit of quantitation, linearity test. Performance characteristic judgements are based on statistical validation techniques.

1.3 Using New or Unfamiliar method

Prior to the use of unfamiliar method, the laboratory should verify and check if the method will be able to meet customer's requirement. The verification should be done on first the published data and secondly on in-house validation data. If the method meets customer's requirement and the laboratory deems competent do perform it, the method should then be approved and be written into a standard operating procedure (SOP) format.

The following additional information should also be indicated:

- The information and laboratory has on the method
- The quality procedure the are in place or the will be required
- The laboratory participation in proficiency testing schemes
- The laboratory conformance to any recognized international standard.

The presence and absence of these highlight issues to be covered during the laboratory starts going through method development and validation

1.4 Method validation Processes

1.4.1 Customer Requirements

Laboratory customers require analytical results that satisfy their needs and expectation. Customer's needs and expectations often are expressed in specification and are collectively referred to as customer's requirements. These requirements may be specified contractually by the customer or by the laboratory itself¹⁵ Be that as it may, customers ultimately determine the acceptability of analysis results. Hence, customers are the reason for all activities done by the laboratory thus, they should be fully integrated when determining data quality requirements.

Because customer's needs and expectations are on continuous changing phase, and because of technological advances, laboratories are required to continual review and revalidate their method to be able to continues meet customer's requirements.

1.4.2 Method Characterization

The method characterization process is a process whereby the laboratory translates customer's requirement into verifiable analytical or statistical data requirements. This requirement should then be check to see if the method can meet them, the actual performance check against these requirements is called method validation process.

1.4.3 Evaluation of published Validation and Verification Data

Method published in international recognized scientific body are often accompanied by insufficient information on the nature and the extent of quality control and assurance employed during validation, such is the indication of the importance of pH or temperature. In some cases, information related to involvement on proficiency testing scheme for the method is not obvious. Therefore it is recommended that these method be validated in side to compensate to vacant information.

1.4.4 Method selection and development

Method validation is closely tied to method development. It is often not possible to determine exactly where method development finishes and validation begins. Many of the method performance parameters that are associated with method validation are in fact usually evaluated, at least approximately, as part of method development. The aim when developing a method is to choose the method that has can best meets the needs of the laboratory and its clients.

The process of selection consists of defining those requirements, searching the technical literature (ASTM, SABS, EPA guides) and then selecting the method whose characteristics best satisfy these requirements.. Method validation should include but not limited to the following:

- Define a quality requirement for the test in the form of the amount of error that is allowable, preferably an allowable total error,
- Select appropriate experiments to reveal the expected types of analytical errors,
- Collect the necessary experimental data,
- Perform statistical calculations on the data to estimate the size of analytical errors,
- Compare the observed errors with the defined allowable error, and
- Judge the acceptability of the observed method performance.

These parameters constitute one of the most important parameters in method validation therefore they need to be understood by the person that will be conducting method validation so that they can be correctly applied.

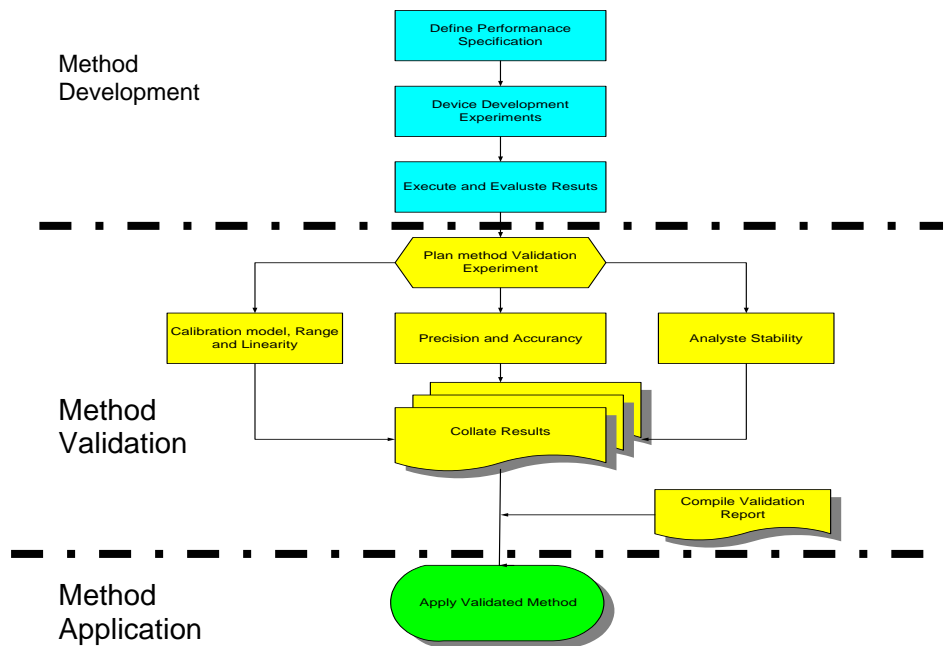


Figure 1: Method Validation Processes

1.4.5 Approval of Method

Method approval involves a verification of the results obtained against an a priori defined requirements. The method should be allowed to run under a trial period for as defined period before it is finally approved. During this period, some parameters might have to be adjusted to align the method with pre-set criteria.

1.4.6 Final acceptance and publication of the method

After the method performance has been checked against pre-set criteria, the methods could be deemed validated against that criteria or it could be found that it does not comply with criteria set. In whichever case, it is a good practice to keep record of the outcomes. In cases when the method fails against the criteria the laboratory might decide to use the method but after refining the criteria and communicating it to relevant stakeholders.

If the method is approved, final records should be compiled and kept for a specific period. The laboratory might find it useful to revalidate the method at a given frequency, especially when new people or equipment is introduced.

1.5 Method Validation Key Performance Parameter

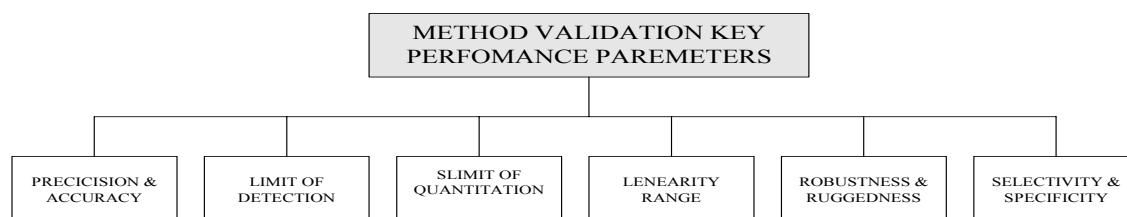


Figure 2: Method validation Key Performance characteristics

The Validation guide line by Waters Right on Time defines validation as “process of providing documented evidence that the method does what it is intended to do” it identifies the following parameters as important key performance parameter in method validation (Fig 2):

- Accuracy and Precision
- Limit of detection
- Limits of quantitation
- Linearity and range
- Ruggedness and Robustness
- Selectivity and Specificity

1.6 Types of Method Validation Schemes

1.5.1 Validation By Using Alternative Method

The validation of an analytical method by using an alternative method is mainly done when a backup instrument exist for the analysis of a particular sample. This is normally done when there is a fully validated method to perform that analysis and the performance of a new method is measured against a fully validated method.

The existing validated method acts as a reference method against which a new method is checked. It should be noted that the validated methods should be checked and quality assurance techniques be put in place to ensure the accuracy of results to be used to validate a new method.

1.5.2 Validation by Using Proficiency testing Schemes

The procedure for conducting Proficiency testing scheme is well detailed in ISO guide 42 and the statistical analysis in ISO 13528 titled “statistical methods for use in proficiency testing by inter-laboratory comparisons”. The international laboratory accreditation cooperation ILAC published guide G13:2000 which details the “Guidelines for the Requirements for the Competence of Providers of Proficiency Testing Schemes”¹⁶.The guide is for providers of proficiency testing schemes who wish to demonstrate their competence by formal compliance with a set of internationally-acceptable requirements for the planning and implementation of proficiency testing schemes.

1.5.3 Validation by Using Certified Reference Materials

Reference material is “materials or substances of whose property value are sufficiently homogeneous and well established to be used for calibration of an apparatus, the assessment of a measurement method, or assessing values for materials” (IUPAC The Orange Book). CRMs provides traceability to an accurate realization of the unit in which it properties are stated.

A method is said to be validated by using reference material when it can provides statistically accurate and validated results when reference material are analysed using that method. Note that to be statistical accurate and validated a method will have to be checked against well defined statistical criteria.

2 MATERIAL AND METHODS

2.1 The Sampling platform

The Boreal Laser HF Analyser was assembled and mounted at the roofvent walk way above pots B113 to B120. The reflector and the instrument were placed at a distance of 43m apart (43m = path length). (Fig 3).

The Isokinetic sampling manifold is located at distance of +/- 3m from the walk way. (Fig 3). The boreal laser shooting was therefore done +/-3m away from the manifold where the Isokinetic sampling points are located.

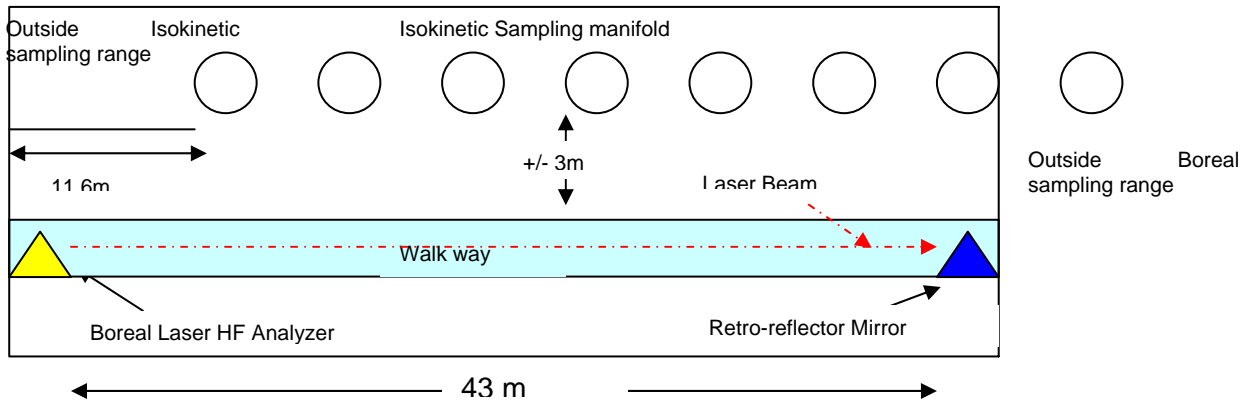


Figure 3 : The roofvent sampling platform: Drawing not on scale

2.2 Sampling Process and Analysis

2.1.1 Isokinetic stack sampling.

A thirty two hour duration sampling of total dust, fluorides gas and particulate was done as per ISO 9096:2003 with the inclusion of 30mg/l of Na_2CO_3 in two impingers for that trapping of gaseous fluorides.

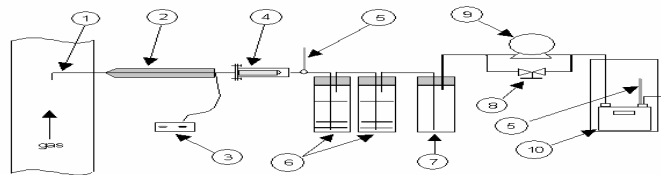


Figure 5: Total Fluorides Emissions Sampling Equipment (ISO 9096:2003)¹⁷

- | | |
|--------------------------|--|
| 1. Sampling Probe Nozzle | 6. Thermometer or thermocouple |
| 2. Heated Sampling Probe | 7. impingers with Na_2CO_3 an empty impinger |
| 3. Temperate controller | 8. Gas flow control valve |
| 4. Thimble holder | 9. Thermometer or thermocouple |
| 5. Thimble holder | 10. Dry gas meter |

2.1.2 The Boreal Laser HF Analyser

The Boreal laser is a real time reading instrument with internal calibration mechanism, memory capacity and downloading function. Downloading and processing of data from Boreal Laser HF analyser was done at Mozal Laboratory.

All Isokinetic samples were taken over a period of 32 hours. The analysis of all samples was done by Mozal Laboratory. The Boreal laser sampling and Isokinetic sampling were done concurrently. The two sets of results were then compared for significance using regression and students t-test as detailed in ^{19, 19}.

3 RESULTS AND DISCUSSION

3.1 Results

The results obtained from the Boreal Laser and Isokinetic Sampling Method were compared by plotting them on column chart (Fig 5)

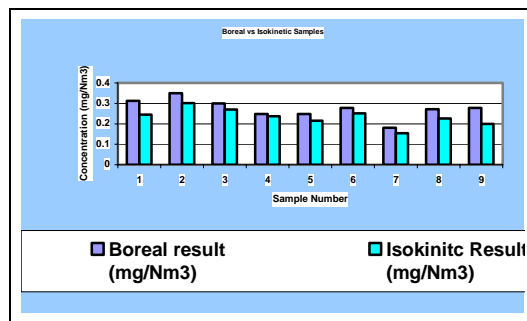


Figure 5: Comparison of the results obtained using Boreal Laser method and Isokinetic method

3.2 Statistical Method Validation

3.1.1 Regression Statistics

Table 2: Calibration data

Standards & Concentration		Calibration Data Specific for sample numbers						AVG
		5	2	4	9	6, 7 & 8	9	
Std No. 1	0	0.0001	0.0003	0.0004	-	(0.0010)	(0.0020)	(0.0004)
Std No. 1	0.05	0.3081	0.2999	0.3087	0.3029	0.3020	0.2686	0.2984
Std No. 3	0.1	0.6033	0.5996	0.6215	0.6198	0.6142	0.6085	0.6112

Note that the statistical data below is based on averages values indicated on table 2.

Table 3: Regression Statistical Data

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.999912011
R Square	0.99982403
Adjusted R Square	0.99964806
Standard Error	0.000938004
Observations	3

ANOVA					
	df	SS	MS	F	Significance F
Regression	1	0.00499912	0.00499912	5681.7817	0.008445247
Residual	1	8.79851E-07	8.798E-07		
Total	2	0.005			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	0.000451653	0.0008517	0.530302708	0.6895875	-0.01037	0.0112734
X Variable 1	0.163498619	0.002169	75.37759386	0.0084452	0.13594	0.1910592

r^2 0.9996 and r 0.9999 indicates good positive linearity
 F-ANOVA = 5682 larger number implying significant linearity

Regression equation

$a = 0.000452$
 $b = 0.1635$

$y = bx + a$
 $y = 0.1635x + 0.000452$

3.1.2 Calibration Uncertainties

$S_{y/x}$ = random calibration uncertainties = 0.000938
 S_b = Uncertainties in the slope = 0.002169
 S_a = uncertainties in the intercepts = 0.000852

Both $S_b < S_{y/x}$ points to good general precision
 $S_a/S_b = 0.002169/0.000852 = 2.546$; the small ration indicated that the selection of standards close to the blank is satisfactory.
 $S_a < S_b$ = the range of standards is wide enough.

3.1.3 95% CL and CI of a and b

Df = 6 $F_{crit(0.05)} = 2.45$
 95% CL of b:
 $b \pm t.S_b$
 $0.1635 \pm 2.45 \times 0.002169$
 0.1635 ± 0.0053
 95 % CI_{ofb} : 0.1582 < b > 0.1688

95% CL of a:
 $a \pm t.S_a$
 $0.000452 \pm 2.45 \times 0.000825$
 0.000452 ± 0.00202
 95 % CI_{ofa} : -0.001568 < a > 0.00247

3.1.4 Calibration Sensitivity

$b = 0.1635 \neq 0$; it points to satisfactory calibration sensitivity.

3.1.5 Limit of detection (LOD) and Limit of Quantitation (LOQ)

$$y_{LOD} = a + 3 S_{y/x}$$

$$y_{LOD} = 0.000452 + 3 \times 0.000938$$

$$y_{LOD} = 0.003266$$

$$y_{LOD} = b \cdot x_{LOD} + a$$

$$x_{LOD} = (y_{LOD} - a) / b$$

$$x_{LOD} = (0.003266 + 0.000452) / 0.1635$$

$$x_{LOD} = 0.0476 \text{ ppm F}^-$$

This method can therefore only detect F⁻ concentration larger than 0.0476 ppm F⁻. all Fluorides concentration for the samples a far above the value

$$y_{LOD} = a + 10 S_{y/x}$$

$$y_{LOD} = 0.000452 + 10 \times 0.000938$$

$$y_{LOD} = 0.00983$$

$$y_{LOD} = b \cdot x_{LOD} + a$$

$$x_{LOD} = (y_{LOD} - a) / b$$

$$x_{LOD} = (0.00983 - 0.000452) / 0.1635$$

$$x_{LOD} = 0.0576 \text{ ppm F}$$

This method can therefore only quantify F⁻ concentration larger than 0.0417 ppm F⁻. all Fluorides concentration for the samples a far above the value

3.1.6 Validation of instrument stability

Statistical process control (SPC) samples are run each time before any analysis is done. The results from the SPC samples are plotted into a chart with 6sigma control limits (Fig. 6). The chart bellow represents more that 250 readings of an SPC sample.

Results that are outside control limits represent problem with the analysis. Production samples could only be analysed after corrective actions that bring the process under control.

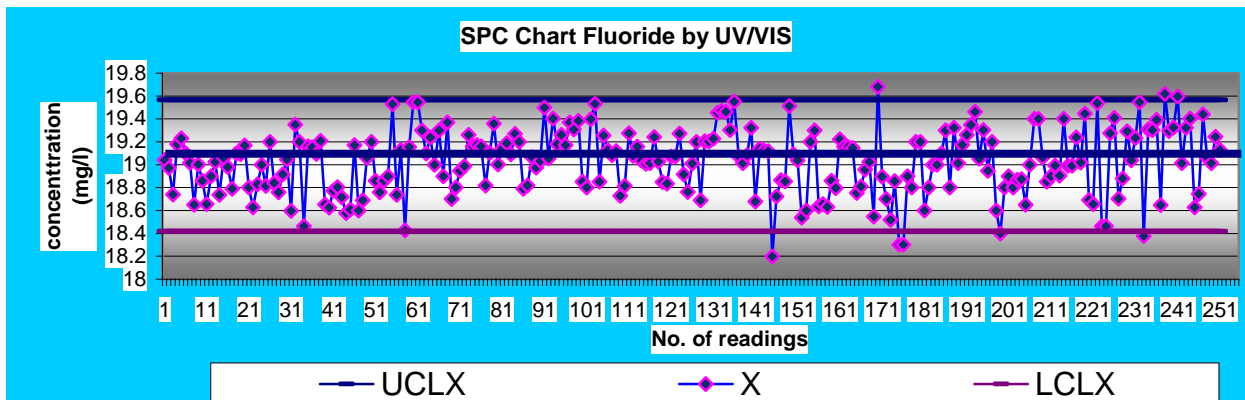


Fig 6 : SPC Chart Fluoride by UV/VIS

3.1.7 Validation of Isokinetic and Boreal Laser HF Results

Table 4: Boreal and Isokinetic results

	Boreal result (mg/Nm3)	Isokinetic Result (mg/Nm3)	Average	STDev
1	0.313	0.246	0.279	0.0472
2	0.350	0.302	0.326	0.0342
3	0.300	0.271	0.285	0.0203
4	0.249	0.238	0.244	0.0079
5	0.248	0.216	0.232	0.0228
6	0.278	0.251	0.264	0.0190
7	0.181	0.154	0.168	0.0193
8	0.272	0.227	0.250	0.0318
9	0.277	0.2	0.239	0.0547

Table 5: Regression Statistical Boreal and Isokinetic results

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.895037627
R Square	0.801092354
Adjusted R Square	0.772676976
Standard Error	0.02254168
Observations	9

ANOVA					
	df	SS	MS	F	Significance F
Regression	1	0.014325	0.014325	28.19221	0.001111689
Residual	7	0.003557	0.000508		
Total	8	0.017882			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	0.04078	0.044617	0.914139	0.391044	-0.0647	0.1463
X Variable 1	0.99841	0.188038	5.309634	0.001112	0.55377	1.4430

Decision rule,

There will be no significant difference between the results obtained using a boreal laser HF analyser and the ones from isokinetic sampling technique if:

r is close to 1

a does not differ significantly (0.05) from zero

b does not differ significantly (0.05) from One

$$r = 0.895 \text{ or } 0.9$$

$$a = 0.0408$$

$$b = 0.998$$

$$S_a = 0.045$$

$$S_b = 0.188$$

$$DF = n-2 = 9-2 = 5$$

$$95\% \text{ CL of } a : a \pm t_x S_a$$

$$95\% \text{ CL of } a : 0.0408 \pm 2.36 \times 0.045$$

$$95\% \text{ CL of } a : 0.0408 \pm 0.1062$$

$$95\% \text{ CI of } a : -0.0654 < a < 0.147$$

Since **0** is part of range of **a**, we are 95 % sure that **a** does not differ significantly from zero.

95% CL of b : $b \pm t \times S_b$

95% CL of b : 0.998 ± 0.0444

95% CL of b : $0.998 \pm 2.36 \times 0.188$

95% CI of b : $0.9536 < b < 1.0424$

Since **1** is part of range of **b**, we are 95 % sure that **b** does not differ significantly from **1**.

3.1.8 Validation by Using Inter-laboratory

Table 6: Inter-Laboratory results

Roofvent HF results			
Laboratories			
Mozal (ppm)	Hillside (ppm)	Set Point (ppm)	Mhlatuze (ppm)
10.4	9.6	10	11.4
13.9	14.9	13	14.3
7.5	6.8	5	5.7

Table 7; ANOVA Boreal and Isokinetic results

Anova: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
Column 1	3	31.8	10.6	10.27
Column 2	3	31.3	10.43333333	16.92333333
Column 3	3	28	9.333333333	16.33333333
Column 4	3	31.4	10.46666667	19.14333333

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.1092	3	1.0364	0.06615	0.976345	4.0662
Within Groups	125.34	8	15.667			
Total	128.45	11				

3.3 Hypothesis testing

H_0 : all samples are from a population with mean μ and a variance of σ^2_0 . This implies that all four results from four different laboratories are from the same samples.

H_1 : Not all samples are from the same population with mean μ and a variance of σ^2_0 . This implies that all four results from four different laboratories are not from the same samples.

$F_{crit0.05}$ 4.066

F_{calc} 0.066

Df 4

3.1.9 Decision Rule:

Reject H_0 if $t_{\text{calc}} > t_{\text{crit}0.05}$

Can not Reject H_0 if $t_{\text{calc}} < t_{\text{crit}0.05}$

Conclusion: Since $t_{\text{calc}} < t_{\text{crit}0.05}$ we can not reject H_0 and conclude that σ^2_0 does not differs significantly form zero.

3.4 Discussion

An array of statistical validation tool like regression statistics, Anova, calibration uncertainty and sensitivity, LoD and LoQ, the SPC charts were used to validate the method. Thought the use of statistics, it has been possible to demonstrate that the method is operating within set validation criteria.

Isokinetic sampling technique is a standard method for gas emission samples in pot rooms. However it has a lot of point where uncertainties could be introduced like the sampling process and laboratory analytical component. The Boreal laser is currently used by a lot of primary smelter to measure HF emission from pot rooms

The validation of actual results from the two sampling techniques was done using regression statistics (0.05) (see section 3.2.7). An $r = 0.9$ has been achieved. It should be noted that although the two method are used to measure HF emission, one is on line method which could possible reduces sampling and analysis uncertainties hence an $r = 9$ is regarded as good value.

Anova was used to validate inter-laboratory HF results between Hillside, Mhlatuze, Set Point Laboratories and Mozal Laboratory (See table 5). Results from these laboratories indicated that there is no significance (0.05) difference between results from the tree laboratory. Hence the conclusion validated Mozal HF results.

4 CONCLUSIONS AND RECOMMENDATIONS

From the aforementioned findings, it can be concluded that there is no significant difference (0.05) between results obtained using the Boreal Laser and the results from Isokinetic sampling method. Hence the boreal laser HF analyser and Isokinitec sampling technique produce similar results (0.05).

4.1 Recommendations

- It is recommended that routine comparisons of the two methods be conducted.
- It is recommended that a similar exercise be done on particulate fluoride
- It is recommended that Mozal asses the possibility of obtaining the Boreal Laser instrument for process control in Reduction, Reduction services and validate Isokinetic sampling results and in some cases to replace the Isokinetic sampling method

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