Vial Leak Test Optimization

Ronald Chávez Salazar
Master of Engineering in Manufacturing Engineering
Carlos J. González Miranda, PhD.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

***Abstract* —** *This paper describes the testing performed to determine the optimum operational parameters that will be used to operate the Mar-Tre Leak Tester for the 12Z vial configurations. Based on the results obtained, the system demonstrated to be capable of detecting leaks on the 12Z vial with 99% reliability and 95% confidence. After optimizing the leak testing process, no escapes or false rejections have been detected. Also, the results obtained confirm that the system has repeatability and reproducibility capabilities.*

***Key Terms* —** *ANOVA, Leak, Optimization, Vials,*

INTRODUCTION

Rochazar is a biomanufacturing company specialized in providing high quality pharmaceutical products. The company is constantly seeking the optimization of their products and processes to supply its customers with the highest standards following all applicable regulations. The company is well recognized for being able to supply the constantly increasing demand of their products. To keep their well-recognized status, the company invest in implementing state of the art technology. One of the most important divisions of the company is the injectable products. They come in two (2) presentations: syringes or vials.

The biopharmaceuticals products are formulated as injectable solutions since the injected solution goes straight into the bloodstream achieving the therapeutic effect promptly. For the Rochazar company, patients are the priority; therefore, being capable of meeting their high needs is imperative. Currently, almost seventy percent (70%) of the high-volume manufacturing is covered by the "Injectables" division.

PROJECT STATEMENT

The company pursues attaining safety, identity, strength, purity, and quality. As part of the initiatives to assure that the vial configurations meet all the acceptance criteria to comply with the standards, an optimization project has been designed to improve the leak testing for all the vial configurations. The same process was followed for each configuration. In this paper, the process for one (1) configuration (12Z) is described.

The components for the production of vials are: vial, stopper, cap, and drug solution.

Figure 1
Vial Components

The test is performed by a Mar-Tre Leak Tester, which is a precision system designed for a nondestructive detection of leaks. The system is designed for the detection of leaks of 10 μm (micron) and above. To test liquid filled vials, the system uses vacuum. The vacuum allows liquids to vaporize and requires the use of sensors to make the precise differential pressure measurements.

PROBLEM STATEMENT

Currently, the vial leak test process has a false rejection rate of thirteen percent (13%). This has a high impact on the company revenues since the estimated financial lost for last year was $17,500,000. This project is mainly focused on reducing loses by optimizing the current leak testing process.

PROJECT METHODOLOGY

Prior to the leak test inspection, the unlabeled liquid filled glass vials are inspected by an automated system. This system inspects for defects on components and in the solution. Vials that fail any inspection to the components are moved to the leak tester.

The vial to be tested is placed into the lower test half of the test chamber. The test chamber (lower and upper halves) is hermetically sealed against the surrounding atmospheric conditions. Leak is detected based on the changes in pressure during the specified test period and conditions. This is registered via the vacuum transmitter sensors. If the vacuum difference, due to a leak in the test sample, exceeds a pre-defined limit during the testing time, the test sample is identified as leaking (bad). All leaking vials are rejected. The test cycle consists of the following five (5) main steps:

- System protection: Short evacuation of the test chamber pressure to an intermediate pressure for the recognition of a big leak and therefore protecting the measuring system from damage.
- Filling: Additional evacuation of the test chamber from intermediate pressure to the final, predefined test pressure.
- Equalizing: Equalization of gas in the test chamber and therefore stabilization of the pressure in the test chamber to shield the leak test itself from temporary equalization flows of gas. Equalization processes must be finished before testing can begin.
- Testing: The testing step itself. Monitoring of changes in the pressure inside the test chamber. The pressure decay during this phase is the basis for detecting small leaks.
- Venting: Venting the test chamber to prepare for the removal of the sample.

The following approach applies to the project for Rochazar Biopharma:

- The vial size to be used is 12Z. This is the vial presentation with the highest manufacturing volume.
- Empty vials will be used since they represent the worst-case scenario.
- The smaller the orifice, the harder it is to detect the leak. Therefore, the minimum detectable orifice size will be used; it is 10µm.
- The standard (certified) leak vials will have the orifice in the neck since it is the hardest detectable area.
- Since the results do not depend on the solution on the vial, the results for a vial size applies to all products using the same vial size.

The critical parameters for the test cycle were identified and will be characterized for creating an optimal recipe for the 12Z vial configuration. These parameters are:

- System protection Delta (mbar)
- Minimum Reference Delta (mbar)
- Initial Reference Delta (Pascal)
- Maximum Reference Delta (Pascal)
- Initial Offset Delta (Pascal)
- Verification Offset Delta (Pascal)
- Empty Chamber Offset (Pascal
- Minimum Vacuum (mbar)
- Filling time (seconds)
- Equalizing time (seconds)
- Testing time (seconds)
- Venting time (seconds)

Process

1. Equipment Setup

1.1 Install the lower and upper testing chamber for the 12Z vial.

1.2 Verify that the inlet compressed air pressure is set as required.

1.3 If applicable, clear any existing alarm condition.

2. Leak Standards Verification

To comply with the required reliability (99%) and confidence (95%), thirty (30) vial standards must be used. The standards are verified to confirm that the air flow through the orifice is equivalent to a 10µ orifice. The verification is performed using a submersion test. The following figure shows the required materials:

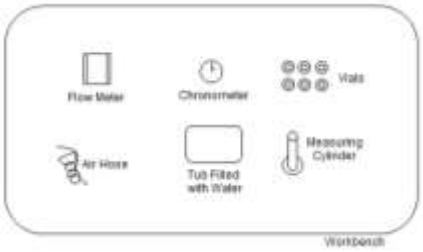

Figure 2
Required Materials

The steps for the submersion test (refer to Figure 3) are described ahead.

Figure 3
Submersion Test

2.1 Fill the tub with DI water.

2.2 Turn on the flowmeter and adjust it to a pressure of 1000 mbar.

2.3 Using the air hose with a needle tip inject air inside an empty and closed vial.

2.4 Immerse the vial, with the hose attached, into the water filled tub.

2.5 Collect the air bubbles coming out of the vial using the measuring cylinder. Keep collecting bubbles for a period of one (1) minute.

2.6 Measure the volume of water (VOW) displaced at the measuring cylinder to obtain the volume of air leaked. To certify that the standard has a 10µ orifice, the displaced volume inside the measuring column must be 1.60 cc ± 10% (1.44 to 1.76 cc).

2.7 The vials that meet the criteria will be used as the leak standards.

3. Initial Recipe Creation

A recipe was created for the 12Z vial using the following settings:

Table 1
Initial Recipe Parameters

Parameter	Unit	Setting
System Protection Delta	mbar	0.4
Minimum Reference Delta	mbar	5.0
Initial Reference Delta	Pascal	0
Maximum Reference Delta	Pascal	1000
Initial Offset Delta	Pascal	0
Verification Offset Delta	Pascal	0
Empty Chamber Offset	Pascal	0
Minimum Vacuum	mbar	2.0
Filling time	seconds	1.00
Equalizing time	seconds	0.50
Testing time	seconds	2.00
Venting time	seconds	0.50

The pressure / vacuum settings used allow taking measurements required for determining actual settings. The times (seconds) set were based on recommendations from the manufacturer.

4. Recipe Optimization

The required results to optimize the recipe will be obtained and the settings will be determined.

4.1 Thirty (30) results will be obtained for each required parameter, they are:

- Self-test (no vial)
- "Empty Chamber" (no vial)
- "Good" vials (non-leak standards)
- "Bad" vials (laser drilled vials)

4.2 Once the results are obtained, the parameters must be calculated using formulas supplied by the manufacturer of the Mar-Tre Leak Tester.

Note: Formulas will not be disclosed for confidentiality purposes.

4.3 Update the recipe parameters with the new values herein obtained.

5. Repeatability and Reproducibility Study

The following statements describe the study:

- Fifteen (15) 12Z leak (10μm) vial standards will be tested.
- Only one (1) gage will be used. It is the leak tester.
- The following are the variables for the study:
  - Operators: 3
  - Vials: 15
  - Repetitions: 3
- The measurements will be taken in the morning, around noon, and in the afternoon.
- The same fifteen (15) samples will be randomly tested by every operator each repetition.
- The results will be evaluated using Minitab [1].

6. Confirmation Runs

6.1 Three (3) runs will be completed. If a run fails, that trial will be stopped. The recipe will be adjusted, and a new trial will be started.

6.2 Trial 1 will be run using the recipe already created (step 2). Identify the results form with trial and run number.

6.3 Since leak is considered a critical defect (leaking vials are discarded), the selected sampling plan is:

Table 2
Sampling Plan

Factor	Criteria
Reliability	99%
Confidence	95%
Sample (N, Good)	300
Defective (Drilled)	30
Escapes	0

Therefore, the acceptance criteria are as follows:

Table 3
Acceptance Criteria

Condition	Status	Expected
Good	Accepted	≥ 299
	Rejected	≤ 1
Defective	Accepted	0
	Rejected	30

6.4 If a run fails, that trial will be stopped. The recipe will be adjusted, and a new trial will be started.

RESULTS AND DISCUSSION

The following sections summarize the results obtained for the processes described in the "Project Methodology" section.

1. Equipment Setup

Prior to testing, the system was setup for the verification of the 12Z vial. No alarm condition was present. The system was set as per normal operation.

2. Leak Standards Verification

Thirty (30) 12Z vials were certified as having a 10μ orifice, as expected. The displaced volume inside the measuring column was within the acceptance range of 1.60 cc ± 10% (1.44 to 1.76 cc).

3. Initial Recipe Creation

The 12Z recipe was created based on the recommendations of the manufacturer.

4. Recipe Optimization

Thirty (30) results were obtained for each required parameter, which are: self-test, empty chamber, good (non-leak standards), and bad (laser drilled). Table 4 summarizes the descriptive statistics [2] for all the results.

Table 4
Measurement Results

Measurement	Average	Std. Dev.
Self-test	291.03	4.08
Empty	35.61	1.44
Good	88.00	2.19
Laser Drilled	484.09	17.01

Figure 4 shows the histograms for the results obtained for the 12Z vial. Table 5 contains the optimized settings for the 12Z recipe.

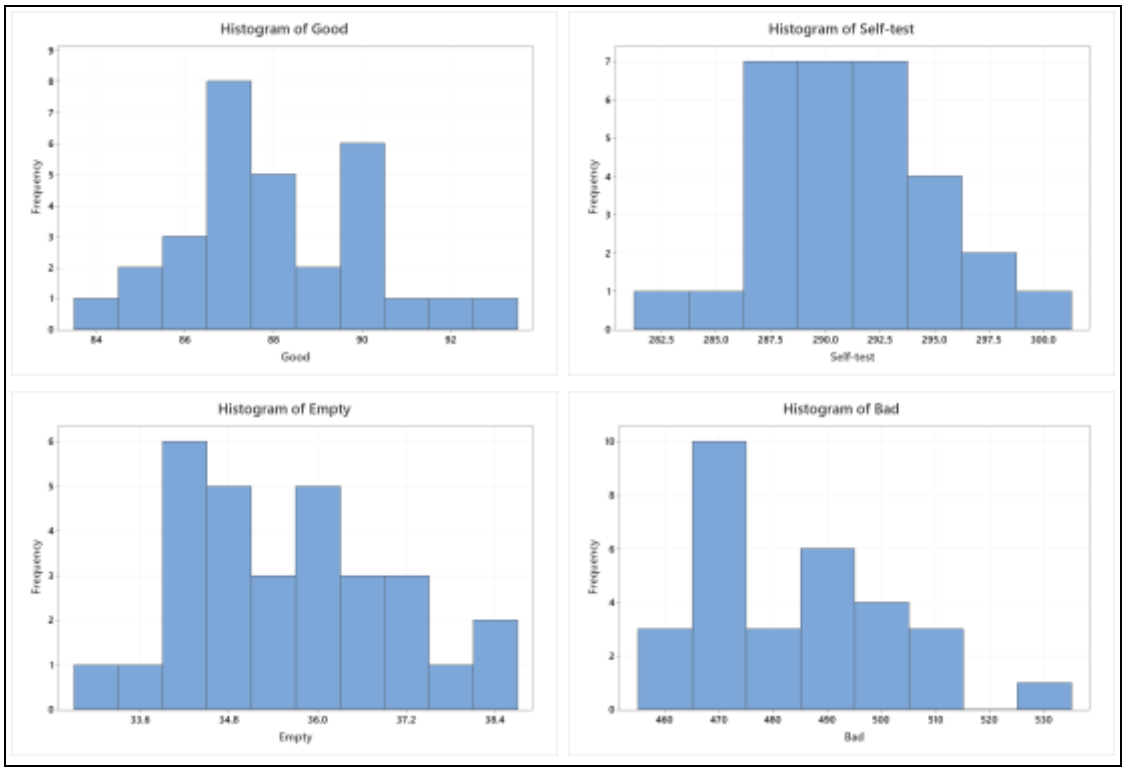

Figure 4
Histograms for 12Z Results

Table 5
Optimized Parameters

Parameter	Unit	Setting
System Protection Delta	mbar	1.5
Minimum Reference Delta	mbar	5.0
Initial Reference Delta	Pascal	139
Maximum Reference Delta	Pascal	383
Initial Offset Delta	Pascal	102
Verification Offset Delta	Pascal	248
Empty Chamber Offset	Pascal	52
Minimum Vacuum	mbar	2.0
Filling time	seconds	1.00
Equalizing time	seconds	0.50
Testing time	seconds	4.00
Venting time	seconds	0.50

5. Repeatability and Reproducibility Study

The results obtained during the Gage R&R study were evaluated using Minitab version 19.2020.1. Figure 5 summarizes the results for the Gage R&R study.

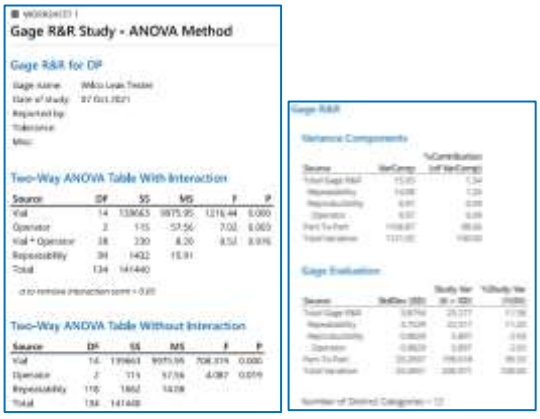

Figure 5
Gage R&R Study Results

The Two-Way ANOVA results are:

- The significance level (α) used for the test was 0.05. With a p-value of 0.976 (greater than α), the vial*operator interaction was removed from the study since it is statistically not significant.

- % Contribution of Variation for the Measurement System
  - 98.66% of the total variability of the measurement system is due to the part-to-part variation.

    Figure 6 displays the differential pressure (DP) results for all operators and repetitions.

Figure 6
Individual Differential Pressure (DP) Readings

    The variation on the results is observed below.
  - Only 1.34% of the total variability is due to the measuring system (Mar-Tre).
- % Study Variance for the Measurement System

  The acceptance criteria [3] are:

< 10%	Measurement system is acceptable
10% - 30%	Measurement system is acceptable depending on the application, cost, and other factors
> 30%	Measurement is unacceptable

  - Total Gage R&R: 11.58%

    This is the sum of the contribution of the repeatability and reproducibility. The total contribution of the leak tester to the measurement system variation is well within the acceptable limits.
  - Repeatability: 11.20%

    This is the variability in measurements when the same operator measures the same part multiple times. The major contribution to the measurement system variation (Total Gage R&R) is within operators (repeatability). This variation is well within the acceptable limits.
  - Reproducibility (Operator): 2.93%

    This is the variability in measurements when different operators measure the same part. It is very low since, for the leak tester, the operator does not perform the measurement.
  - Part-to-Part: 99.33%

    The major contribution to the study variability is made by the part-to-part variation. There is no acceptance criterion for this variation since it depends on the vials used.
- Number of Distinct Categories (NDC)

  The number of distinct categories determines the ability of the measurement system to detect a difference in the measured variable (DP). It represents the number of non-overlapping confidence intervals that span the range of product variation. The acceptance criteria [3] are:

≥ 5	Adequate measuring system
2	Data can be divided into two (e.g. Low and High)
3	Data can be divided into three (e.g. Low, Medium and High)
< 2	Measurement system has no value for controlling the system

  The result indicates that:
  - The NDC at 12 is well within the acceptable limits.
  - The measurement system is acceptable.

The following plots display the results for the study:

- Components of Variation

  Part-to-Part is the major contributor to the measurement system variation. The leak tester (Gage R&R) is within the acceptance criteria of the measurement system analysis.

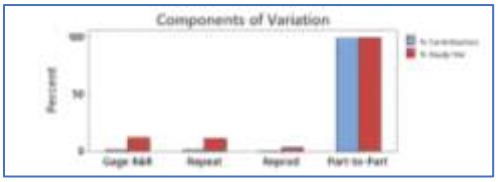

Figure 7
Components of Variation

- Differential Pressure by Vial

  This graph clearly demonstrates the variation on the results for the different vials.

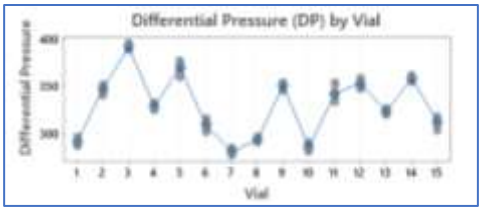

Figure 8
Differential Pressure by Vial

- R Chart by Operator

  This chart plots, for each operator, the difference between the largest and smallest measurements for each vial (1 to 15) to evaluate how consistent each operator is (repeatability). For operator 3, one (1) point fell outside the limits. The chart proves that the repeatability of the system is in control; therefore acceptable.

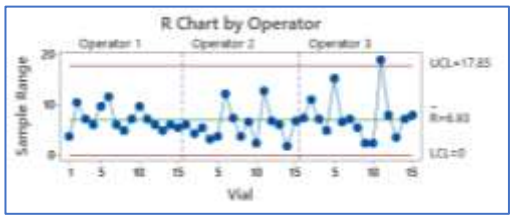

Figure 9
R Chart by Operator

- Differential Pressure by Operator

  This chart indicates that the mean measurements for the three (3) operators are similar. Therefore, the results between operators are not a significant source of variation for the measurement system. The measurement system has capacity to reproduce results (reproducibility).

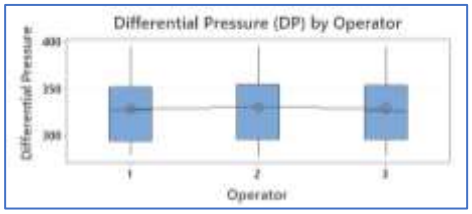

Figure 10
Differential Pressure by Operator

- Xbar Chart by Operator

  The average measurement of each part is plotted for each operator to evaluate the part-to-part variation with the repeatability component. The plot demonstrates that the major source of variation is part-to-part and the repeatability of the system is acceptable.

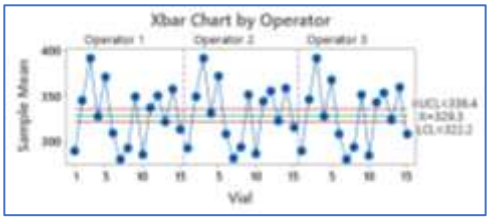

Figure 11
Xbar Chart by Operator

- Vial * Operator Interaction

  This plot displays the average measurements by each operator for each part. The three (3) overlayed plots are similar. The results for a part are not related to which operator measured it. Therefore, the vial*operator interaction is not significant.

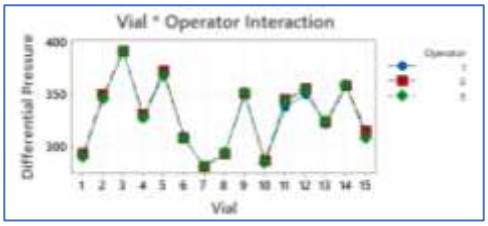

Figure 12
Vial * Operator Interaction

The results for the Gage R&R study demonstrate that the leak tester is acceptable for its intended function. The measurement system has the capacity to repeat and reproduce results (repeatability and reproducibility).

CONFIRMATION RUNS

A trial, consisting of three (3) runs, was performed to verify the recipe. Each run consisted of randomly testing three hundred (300) good vials and thirty (30) 10 µm leak standards. To achieve 99% reliability with 95% confidence, all the leak samples (30) must be rejected. Table 6 shows the results for this section.

Table 6
Results for Confirmation Runs

Trial No.	Run	Good Vials (300)		Drilled Vials (30)	
		Accepted (Expected: ≥ 299)	Rejected (Expected: ≤ 1)	Accepted (Expected: 0)	Rejected (Expected: 30)
1	1	299	1	2	28
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
2	1	300	0	1	29
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
3	1	300	0	0	30
	2	300	0	0	30
	3	300	0	0	30

- Trial 1

Two (2) leak vials were accepted. After evaluating the settings, the following parameter was modified, and a new trial was started.

Parameter	Previous	Change
Equalizing time	0.50	1.00

- Trial 2

One (1) leak vial was accepted. After evaluating the settings, the following parameter was modified and a new trial was started.

Parameter	Previous	Change
Testing time	2.00	4.00

- Trial 3

All three (3) runs met the acceptance criteria. Using thirty (30) leak results and the first thirty good results for the first run, the following graph was created to show the results trend (for reference).

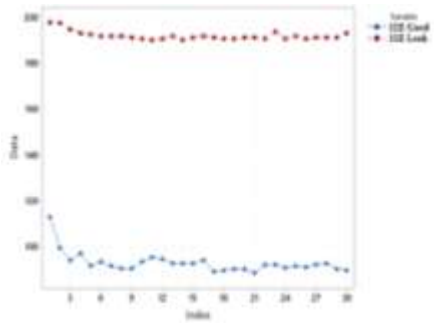

Figure 13
Time Series Plot

There is an evident separation between good and leak results, indicating the capability of the measurement system to differentiate between defects and acceptable units.

The recipe is considered acceptable. Table 7 shows the final parameter settings for the 12Z recipe.

Table 7
Final Settings for the 12Z Recipe

Parameter	Unit	Setting
System Protection Delta	mbar	1.5
Minimum Reference Delta	mbar	5.0
Initial Reference Delta	Pascal	139
Maximum Reference Delta	Pascal	383
Initial Offset Delta	Pascal	102
Verification Offset Delta	Pascal	248
Empty Chamber Offset	Pascal	52
Minimum Vacuum	mbar	2.0
Filling time	seconds	1.00
Equalizing time	seconds	0.50
Testing time	seconds	4.00
Venting time	seconds	0.50

CONCLUSIONS

After successfully completing all testing and analyzing the results, it is concluded that the Mar-Tre Leak Tester is suitable for detecting leaks of 10μm or higher for the 12Z vials.

The studies conducted demonstrate that the system can maintain its precision, robustness, sensitivity, and system suitability. The system is capable of consistently differentiate between good (non-leak) and bad (leak) vials as intended. Also, the results obtained by the system has repeatability and reproducibility capabilities.

The optimum parameters for the operation of the machine were obtained. After optimizing the leak testing process, no escapes or false rejections have been detected.

REFERENCES

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[3] Automotive Industry Action Group (AIAG), *Measurement System Analysis, Reference Manual*, 4th ed, Southfield, MI: Automotive Industry Action Group, June 2010.