Vial Leak Test Optimization

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Abstract

The research presented in the poster, was generated to determine the optimum operational parameters that will be used to operate the Leak Tester machine to detect leaks in 12Z vial configurations.

Based on the results obtained, the system demonstrated:

- Capability 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.
- The obtained results confirm that the system has repeatability and reproducibility capabilities.
- The Leak Tester is suitable for detecting leaks of 10µm or higher for the 12Z vials.

Introduction

- Rochazar is a biomanufacturing company specialized in pharmaceutical products.
- The company is well recognized for being able to supply the constantly increasing demand of their products.
- One of the most important divisions of the company are: syringes or vials.
- The company is constantly seeking the optimization of their products and processes.
- This project is mainly focused on reducing loses by optimizing the current leak testing process.

Background

This project is mainly focused on reducing loses by optimizing the current leak testing process.
The vial inspection process are the following:

- Vials are inspected by an automated system
- Vials that fail any inspection to the components are moved to to manual inspection.
- Vial are moved to leak test.
  - The vial leak test is performed by a Mar-Tre Leak Tester:
  - The vial to be tested is placed into test chamber.
  - The test chamber (lower and upper halves) is hermetically sealed.
  - Leak is detected based on the changes in pressure during the specified test period and conditions.
- Packaging

Problem

- Vial leak test process has a false rejection rate.
- High impact on the company revenues since the estimated financial lost for last year was $17,500,000.

Methodology

The following approach was developed as part of the project development:

Vial Configuration

- The vial size to be used is 12Z.
- Empty vials will be used for this test.
- The minimum detectable orifice size will be 10µm.
- The standard (certified) leak vials will have the orifice in the neck area.
- The test results 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.

Leak Standards Verification

- Reliability / confidence level: 99% / 95%
- Required leak samples: thirty (30) vial standards
- The standards were verified and confirmed that the air flow through the orifice is equivalent to a 10µ orifice.
- The verification is performed using a submersion test.

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

Recipe Optimization

- Thirty (30) results were obtained for each required parameter, they are: Self-test (no vial), “Empty Chamber” (no vial), “Good” vials (non-leak standards) and “Bad” vials (laser drilled vials)
- The recipe parameters were updated with the values obtained.

Repeatability and Reproducibility 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

Confirmation Runs

- A trial, consisting of three (3) runs, must be successfully (all criteria met) completed using the recipe already created.

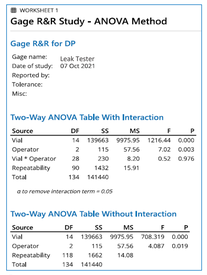
Results and Discussion

The obtained results are as follows:

- **Equipment Setup**
  - System set as per normal operation
- **Leak Standards Verification**
  - Thirty (30) 12Z vials having a 10µ orifice
  - Acceptance range of 1.60 cc ± 10% (1.44 to 1.76 cc)
- **Initial Recipe Creation**
  - Based on the manufacturer’s recommendations
- **Recipe Optimization**
  - Thirty (30) results for self-test, empty chamber, good (non-leak standards), and bad (laser drilled).
  - Results:

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

- **Repeatability and Reproducibility Study**
  - Minitab version 19.2020.1
  - Two-way ANOVA results:



WORKSHEET 1

Gage R&R Study - ANOVA Method

Gage R&R for DP

Gage name:
Date of study: 07 Oct 2021
Reported by:
Tolerance:
Misc: Leak Tester

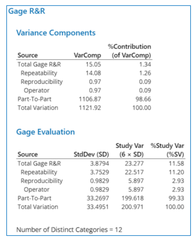
Two-Way ANOVA Table With Interaction

Source	DF	SS	MS	F	P
Vial	14	139663	9975.95	1216.44	0.000
Operator	2	115	57.56	7.02	0.003
Vial * Operator	28	230	8.20	0.52	0.976
Repeatability	90	1432	15.91		
Total	134	141440			

α to remove interaction term = 0.05

Two-Way ANOVA Table Without Interaction

Source	DF	SS	MS	F	P
Vial	14	139663	9975.95	708.319	0.000
Operator	2	115	57.56	4.087	0.019
Repeatability	118	1662	14.08		
Total	134	141440			



Gage R&R

Variance Components

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	15.05	1.34
Repeatability	14.08	1.26
Reproducibility	0.97	0.09
Operator	0.97	0.09
Part-To-Part	1106.87	98.66
Total Variation	1121.92	100.00

Gage Evaluation

Source	StdDev (SD)	Study Var (6 × SD)	%Study Var (%SV)
Total Gage R&R	3.8794	23.277	11.58
Repeatability	3.7529	22.517	11.20
Reproducibility	0.9829	5.897	2.93
Operator	0.9829	5.897	2.93
Part-To-Part	33.2697	199.618	99.33
Total Variation	33.4951	200.971	100.00

Number of Distinct Categories = 12

    - vial*operator interaction is statistically not significant (p-value of 0.976 > α)
    - Major source of variation: vial (part-to-part, 98.66%)
  - **Total Gage R&R: 11.58%**
    - Repeatability: 11.20%
    - Reproducibility: 2.93%
  - **Part-to-Part: 99.33%**
    - The major contribution to the study variability is the vials.
  - **Number of Distinct Categories (NDC): 12**
    - Ability of the measurement system to detect a difference in the measured variable (DP)
    - Acceptance criteria: NDC ≥ 5
- **Confirmation Runs**
  - Three (3) runs per trial
  - Randomly test three hundred (300) good vials and thirty (30) 10 µm leak standards per run
  - Reliability / confidence level: 99% / 95%
  - All the leak samples (30) must be rejected
  - Parameters adjusted for trials 1 and 2
  - Acceptance criteria met for trial 3
  - The recipe was updated

Conclusions

After successfully completing all testing and analyzing the results, it is concluded that:

- The Leak Tester is suitable for detecting leaks of 10µm or higher for the 12Z vials.
- 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.
- The results obtained by the system has repeatability and reproducibility capabilities.
- After optimizing the leak testing process, no escapes or false rejections have been detected.
- The system operates with the requires level of reliability and confidence.

Future Work

- Automated Vial Inspection system Optimization

Acknowledgements

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Non-Amgen