Case Study: Test Method Development and Validation for 2 mL Glass Vials Containing 0.70 mL of Drug Product using HVLD

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Outline

- Method Development Strategy
- Aim of the study
- Methods and Materials
- Experimental Setup
- Results
- Conclusion

Method Development Strategy

Container and Product Details

- Container Type: Vial, Prefilled Syringe, Ampoules
- Container Material: Glass, Plastic, other etc.
- Closure Type: Rubber stopper, Aluminum Cap
- Drug product detail: Formulation, Liquid small or large molecule (Protein),
- Size of the container,
- The liquid fill volume of the container
- Materials
  - Negative controls (non-defective containers)
  - Positive controls: Laser drilled holes at 2, 5, 10, 15 and 20 μm

Method Development Strategy

Instrumental (HVLD) Details

- Equipment Qualification (IQ, OQ and PQ)
- Container specific equipment:
  - sample holder
  - resistor block
- Instrumental parameters:
  - voltage
  - gain sensitivity
  - speed, rotation
  - motion profile

Method Development Strategy

- **Validation Parameters <USP 1207.1>**
  - Specificity
  - LOD
  - Accuracy and Range
  - Precision (Repeatability, Intermediate Precision)

Aim of the Study

To develop and validate a test method for an optimal CCIT for 2 mL vials containing approximately 1.0 mL fill of drug product using HVLD

2 mL vial filled with 0.70 mL DP

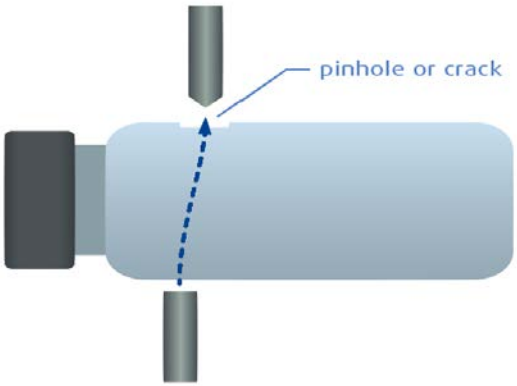
PTI E-scan 655 HVLD

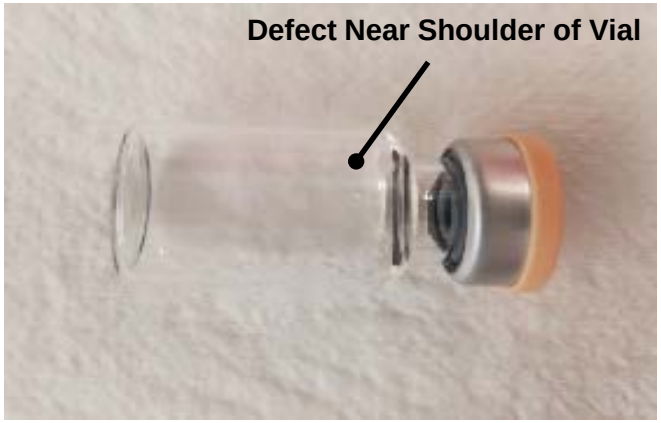
Method and Materials

- Drug Product (DP)/ Formulation buffer
- 2 mL empty vials (45 units)
- 2 mL vial cap (45 units)
- 2 mL vial stopper (45 units)
- Negative controls: 2 mL Vials (30 units)
- Positive Controls: 2 mL Vials with laser drilled holes at 2, 5 and 10 μm (10 units each)

Experimental Setup

- Negative Control: 2 mL Vials (30 units)
- Positive Control: 2 mL Vials with holes at 2, 5 and 10 μm (10 units each)
- In total 90 Positive and 90 Negative Control measurements
- 3 experimental replicates, 3 different days, 2 analysts

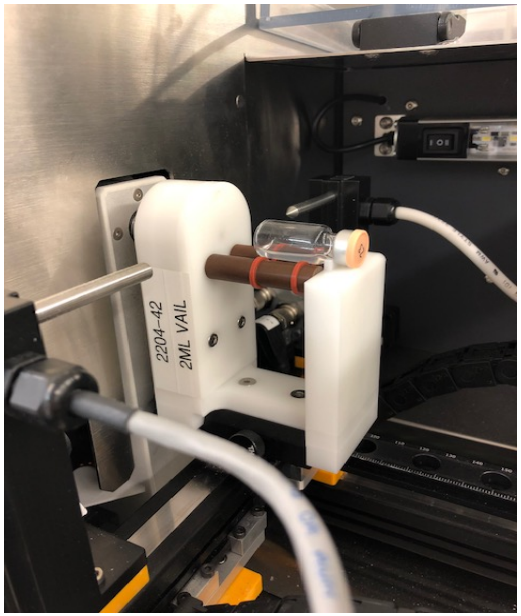




Defect Location at the Shoulder of the Vial

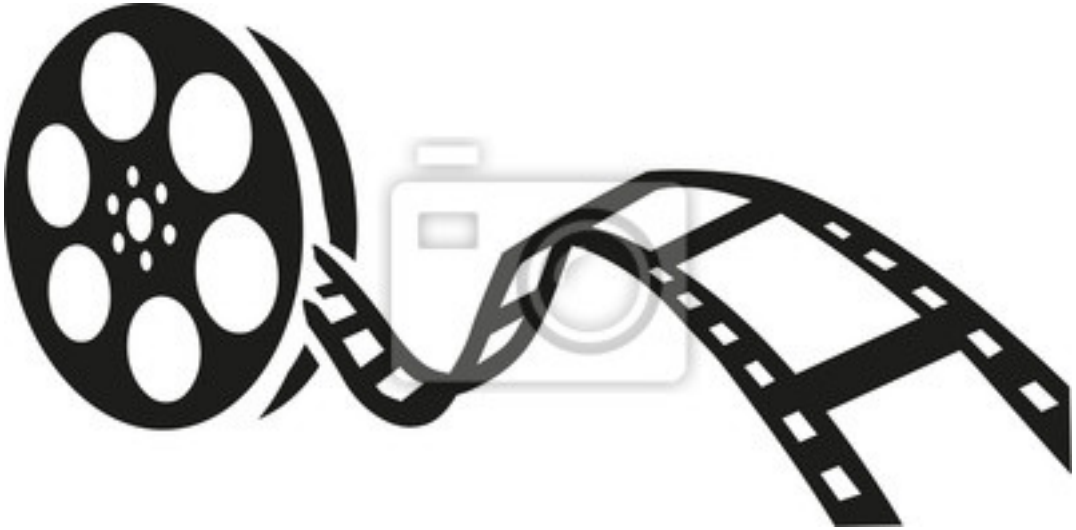
Optimization of HVLD Parameters

Parameter	Description
High voltage	13 kV
Sensitivity	55%
Rotation	300 RPM
Speed	8 mm/s



Motion Profile				
Step	**X**	**Y**	**V**	**W**
1	43.5	50.0	32.0	50.0
2	43.5	5.1	32.0	8.4
3	43.5	5.1	31.5	8.4
4	43.5	5.1	32.0	8.4
5	41.8	5.1	32.0	8.4
6	41.8	8.0	32.0	8.4
7	32.3	8.0	32.0	8.4
8	21.2	8.0	16.2	8.4
9	12.7	8.0	24.8	8.4
10	12.7	5.3	24.8	8.4
11	12.7	5.3	25.3	8.4
12	12.7	5.3	24.8	8.4

Optimization of HVLD Parameters

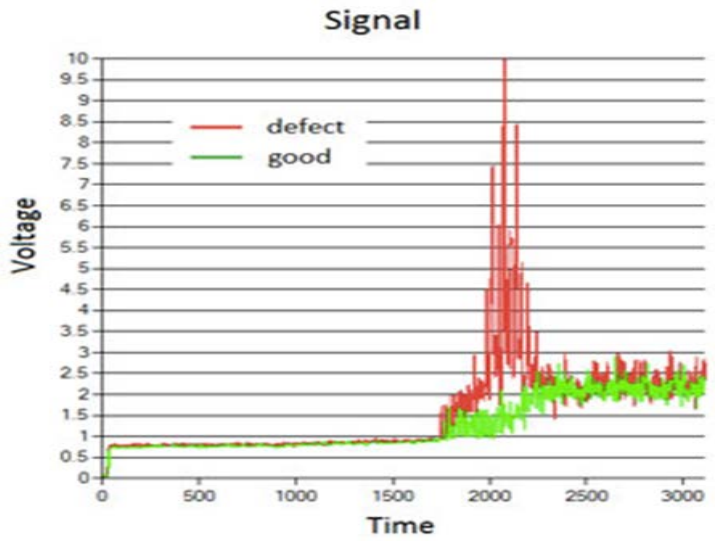


Validation Parameters

LOD: the smallest breach in the vials allowing a "consistent differentiation" from voltage observed in non-defective vials

- LOD was established as 2 μm
- Confidence 95%

Specificity: the ability to differentiate between leaking and non-leaking vials, despite interfering factors that may cause false detection.



Example of HVLD-scanning profile result

Determination of Rejection Threshold

n=3, 90 measurements*	
Parameters	**Negative controls**
Average	2.66 VDC
StdDev	0.26
Mean + StdDev	2.92 VDC
Mean + 6xStdDev	4.19 VDC
Mean + 10xStdDev	5.22 VDC
Confidence 95%	0.05 VDC
Confidence Low	2.61 VDC
Confidence High	2.71 VDC
Minimum	2.36 VDC
Maximum	3.97 VDC

Rejection Threshold: 4.19 VDC

LOD Criterion: Smallest leakage rate (or leak size) that a test method can reliably detect.

*All negative controls passed

Validation Parameters

Precision: the ability of the method to yield reliable and repeatable date (n=3, 2 analysts, in total 90 measurements for positive and negative vials)

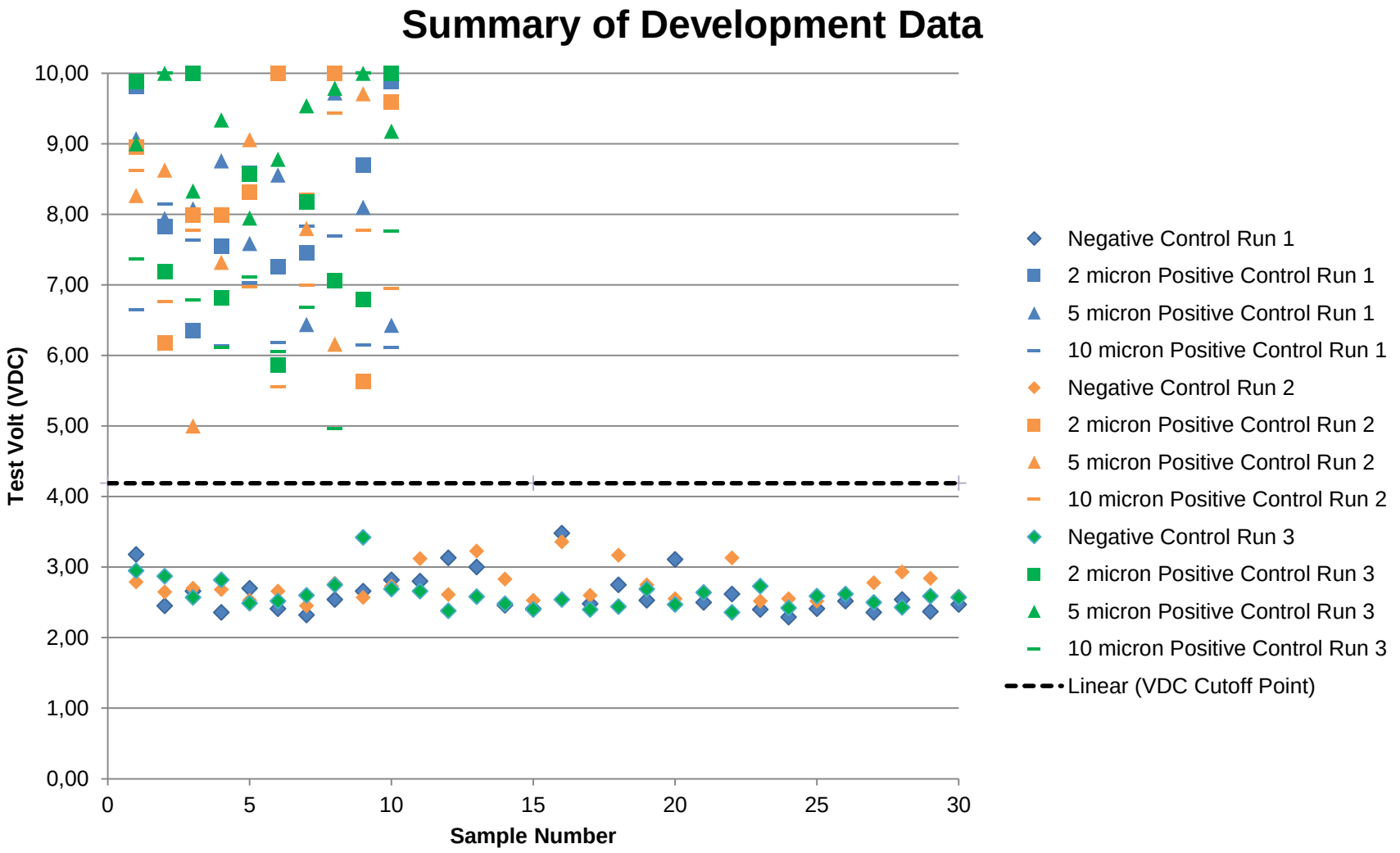
Accuracy: the ability to differentiate samples with defects greater than or equal to the established LOD from samples with defects less than the established LOD, using voltage measurements.

Range: the range over which the method has shown to have acceptable precision accuracy from the established LOD up to the greatest defect size tested

Acceptance criteria:

- The voltage results for every positive control and gross leak vial tested is ≥ Rejection threshold (4.19 VDC) (for Accuracy and Precision)
- The voltage result for every negative control vial tested is less than 4.19 VDC (for Accuracy and Precision)

Results of Development Runs



Positive Control Results

n=3, total 90 measurements*			
Parameters	**2 μ Defect (n=30)**	**5 μ Defect (n=30)**	**10 μ Defect (n=30)**
Average	8.22 VDC	8.49 VDC	7.24 VDC
StdDev	1.38	1.27	1.20
Mean - StdDev	6.84 VDC	7.22 VDC	6.04 VDC
Mean - 2xStdDev	5.46 VDC	5.94 VDC	4.84 VDC
Confidence 95%	0.49 VDC	0.46 VDC	0.43 VDC
Confidence Low	7.73 VDC	8.03 VDC	6.81 VDC
Confidence High	8.71 VDC	8.94 VDC	7.67 VDC
Minimum	5.63 VDC	5.00 VDC	4.96 VDC
Maximum	10.00 VDC	10.00 VDC	10.00 VDC

*All tested positive controls passed

Conclusion

- The method was specific to differentiate non-defective (negative controls) vials from defective (positive) ones
- The method LOD was determined to be 2 μm
- The rejection threshold was determined to be 4.19 VDC
- The data showed acceptable accuracy and precision
- For gross leak testing, stopper defects (fiber leaks) are not recommended, instead cracks on the body of the vials are recommended to be used as gross leaks to evaluate the range of the method.

References

<1207> Package integrity evaluation –Sterile products

<1207.1> Package integrity in the product life cycle –Test method selection and validation

<1207.2> Package integrity leak test technologies

Acknowledgments

- Jennifer Roark, B.S., Manager Chemistry & Container Testing, Eurofins Lancaster Laboratories
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THANK YOU!