

A Paradigm Shift in Container Closure Integrity of Parenteral Products

MICROCURRENT HVLD TECHNOLOGY

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Container Closure Integrity (CCI) is defined by whether a container maintains the sterile barrier. If there is a leak or breach of the sterile barrier, environmental contaminants can rapidly convert a life saving treatment into a microbial soup. Parenteral products are the highest risk of all package formats. Vials, ampoules and prefilled syringes have the highest potential for microbial growth, and the risk to the end patient amplifies the focus needed on CCI for these applications.

Historically there have been a variety of test methods used for parenteral CCI testing. The use of less sensitive and archaic methods has evolved to better procedures and newer technologies. There is still a level of misinformation and a reliance on probabilistic solutions for CCI testing of high risk parenteral products. Regulatory bodies have initiated the shift to more deterministic test methodologies that can be controlled, calibrated and provide a definitive determination of CCI.

High voltage leak detection (HVLD) has been a common technology on the market for decades. The latest evolution of HVLD, PTI's patent pending MicroCurrent technology, aims to achieve a high level of CCI assurance across the entire range of parenteral products. High voltage leak detection is a method included in USP 1207 as a deterministic test methodology and is an established and reliable solution for all liquid filled parenteral products.

TRADITIONAL METHODS

The dye ingress and microbial ingress methods have been traditional methods deployed for parenteral CCI. The ability to detect defects varies greatly, and there is no global standard to perform these methods. USP 1207 has clearly outlined these methods as probabilistic and for good reason.

While vials and ampoules do have the physical requirements to perform an ingress test, the method does not provide the certainty of detecting critical defects. For package formats such as a prefilled syringe or cartridge, the lack of internal headspace makes these methods even less effective. The general probabilistic nature of these methods is exacerbated by the difference in physical properties of each package type. With a method that has a variable probability of detection there is one fundamental question, how can it be validated? The simple answer is that both the blue dye and microbial methods struggle to produce validation worthy test results befitting of high risk packaging applications.

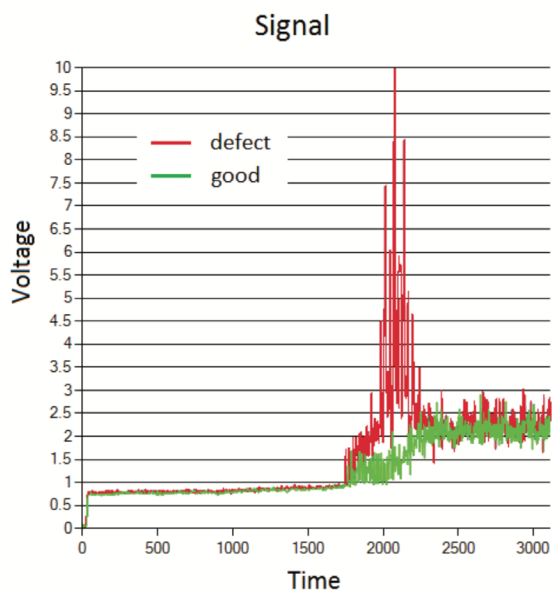
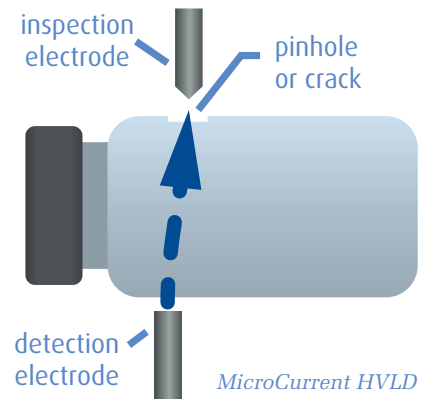
The blue dye ingress method and the microbial ingress method can be largely described as qualitative in nature, with a simple pass/fail result. The destructive nature of the test makes test results finite despite the probabilistic nature of the result, making it almost certain that at some point batch release data will be inaccurate, sending good product out to market or issuing a flurry of remedial actions based on a false reject.

ADVANCES IN DETERMINISTIC PARENTERAL CONTAINER CLOSURE INTEGRITY

HVLD operates on the simple property of electrical current. The package barrier must be non-conductive and would resist voltage from passing through, while the package contents should generally be able to carry voltage. Liquid products with a conductivity of 5 micro-siemens and greater meet the requirement for PTI's MicroCurrent HVLD.

The container is placed horizontally on a rotating stage. While rotating the container, high voltage is applied to one side of the container and a ground probe on the opposing side.

If the package has no leak, the two container walls (high voltage side and ground side) provide full electrical resistance and no significant current is measured passing through the vial. If there is a micro-leak or crack in one of the container walls, the break-down resistance is reached and the current passes through.



HVLD is the only leak detection technology that does not require mass to pass through a defect site, requiring only the passage of electricity through a crack. This characteristic makes HVLD sensitive to leaks in which most leak test solutions cannot identify.

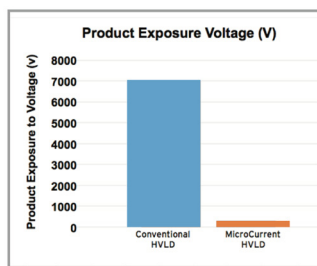
PTI's MicroCurrent HVLD technology uses unique voltage characteristics to inspect a wide range of parenteral products. Traditional HVLD has proven to be an effective solution for standard parenteral products, but requires a level of conductivity for the liquid contents of the package. PTI's MicroCurrent HVLD greatly increases the range of liquid conductivity that can be tested, with the technology capable of testing water for injection (WFI) and other liquids in the single digit micron range.

The MicroCurrent HVLD reduces voltage exposure to the product to less than 5% of the voltage exposure experienced when testing with comparable HVLD solutions. Reducing exposure voltage not only reduces any risk that the voltage poses to the product, but also greatly reduces the production of Ozone during operation when compared with traditional HVLD solutions. Ozone in the headspace of a container can be detrimental to the product, and in the operating environment can affect respiratory health. Experiments have shown that PTI's MicroCurrent HVLD produces essentially no Ozone.

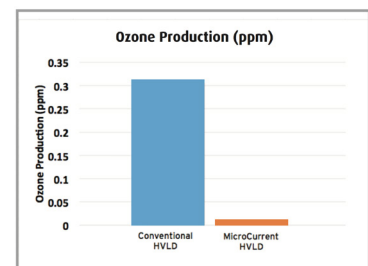
DETERMINISTIC, QUANTITATIVE TEST METHODS PROVIDE:

- Hard traceable data
- Discrete pass/fail limits
- The ability to calibrate a system
- Avoidance of subjective influences in results
- A reliable test method that can be validated and rolled out globally

Product HV Exposure



Ozone Creation



	Conventional HVLD	MicroCurrent HVLD
Exposure Voltage (V)	7000	300
Ozone Production (ppm)	0.305	0.006