Comparison of Direct and Indirect Container Closure Integrity (CCI) Testing Methods for Autoinjectors

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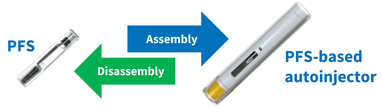
Abstract/Introduction

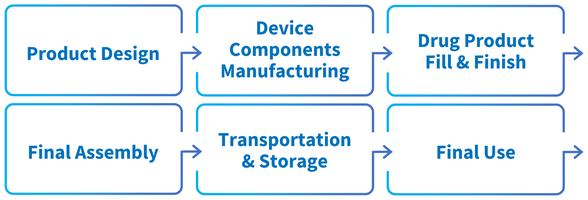
Necessity for CCIT

- Container closure integrity testing (CCIT) is a crucial process that ensures the quality and safety of a drug product throughout its shelf life.
- Regulatory authorities require the CCIT results combined with sterility data.

CCIT Challenges for PFS-Based Autoinjectors and Other Combination Products

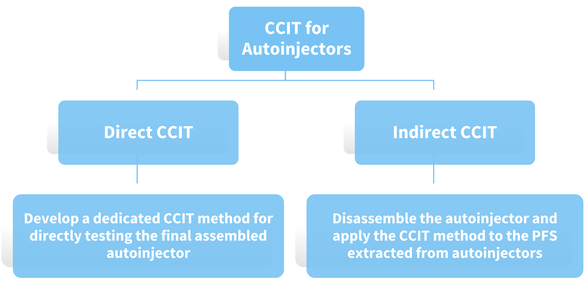
- The primary packaging that contains the drug is integrated with a rigid device shell or housing.
- The CCIT methods for pre-filled syringes (PFS) and vials are difficult to apply to assembled autoinjectors.
- Specialized direct or indirect CCIT methods for autoinjectors must be developed and validated.





CCI must be maintained and evaluated throughout the lifecycle of any drug-device combination product

Methods



Typical CCIT Methods in WuXi Biologics

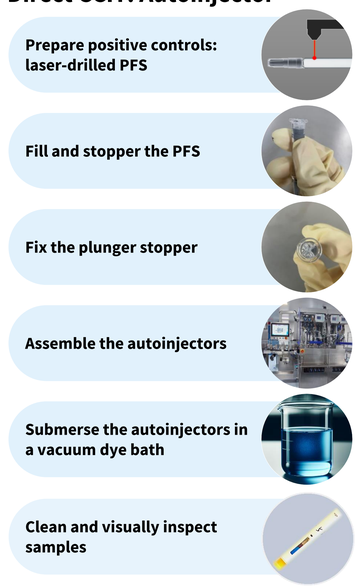
Dye Ingress (Probabilistic)
Submerge the package in a dyed solution, and then observe whether any dye penetrates the package.

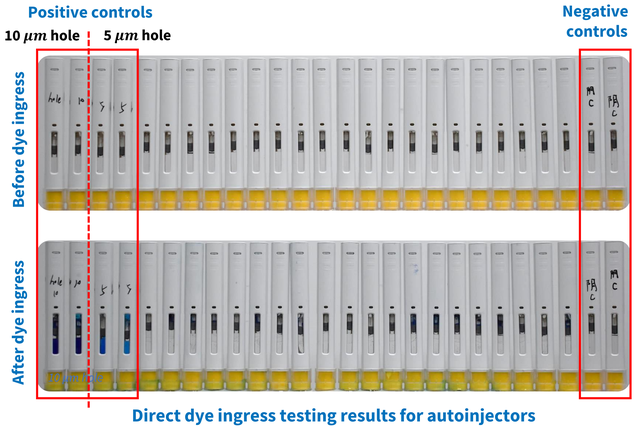
(Stauffer 2020)

Vacuum Decay (Deterministic)
Detect leaks by measuring the change in pressure within a sealed chamber.

Results

Direct CCIT: Autoinjector





Direct dye ingress testing results for autoinjectors

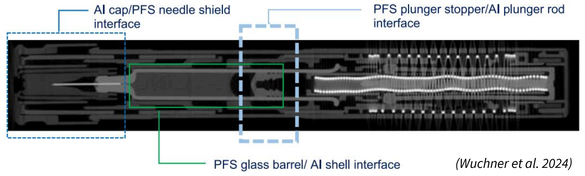
- Dye ingress testing is a practical method for assembled autoinjectors.
- Larger laser-drilled holes in a PFS increase dye penetration (darker color) in positive control samples with 5 µm and 10 µm holes, as per USP <1207>. Dye cannot penetrate into the PFS in the autoinjector without vacuum treatment.
- CCI of the tested autoinjectors meets the acceptance criteria.
- To enhance the reliability of the test results and minimize the occurrence of false negatives, securing the stopper in place before testing is advisable.

Indirect CCIT: Autoinjector Disassembly + CCIT for Extracted PFS

- A customized disassembly procedure for autoinjectors is tailored per product design and risk assessment.
- Disassemble the autoinjector without compromising the CCI of the internal PFS, then conduct CCIT on the PFS.

Examples of the assembly process and risks

Assembly Process	Potential Failure Mode	Failure Cause
Gripping the PFS	• Movement of the stopper can lead to leakage	• Gripper may touch and push the stopper
Assemble the PFS into the autoinjector	• Loose rigid needle shield (RNS) • RNS comes off	• Movement of the RNS caused by the friction when the RNS fits into the cap remover
Insert the drive unit	• Movement of the stopper can lead to leakage	• The plunger rod may touch/push the stopper

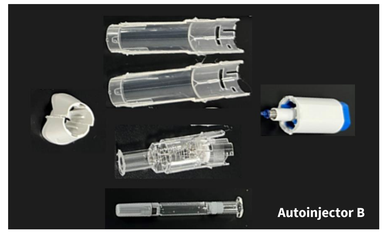


(Wuchner et al. 2024)

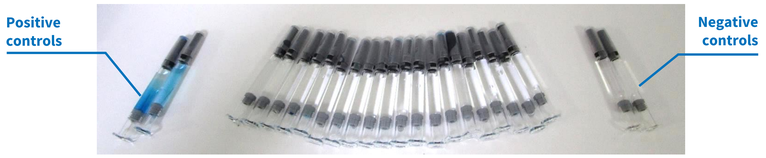
Examples of the corresponding disassembly strategy

Disassembly Process	Purpose
Remove the drive unit	• Prevent accidental activation of injection spring • Eliminate the possibility of stopper movement
Separate the cap of autoinjector from the PFS	• Eliminate the contact surface between the cap and the RNS, thereby reducing the possibility of RNS loosening
Detach PFS from the body of the autoinjector	• Completely disassemble the autoinjector, and then extract the PFS

Disassembled Autoinjectors



CCIT for PFS Extracted from Autoinjectors



PFS Extracted from Autoinjector B

	Vacuum Decay	Dye Ingress	Microbial Challenge Test
PFS Extracted from Autoinjector	Pass	Pass	Pass

- Different CCI tests conducted on PFS extracted from autoinjectors have consistently demonstrated successful results.
- These outcomes validate that the developed disassembly method is effective and does not compromise the CCI of the assembled autoinjectors.
- The disassembly strategy, proven effective across various autoinjectors, can extend to additional models.

Conclusion and Future Work

- Both direct and indirect methods are successfully developed for autoinjector CCIT.
- Although practical for autoinjectors, the dye ingress method is probabilistic and not PDA-recommended. Other direct CCIT methods require specific development and testing chambers.
- Effective CCIT bridging from PFS to autoinjectors is achieved through proper disassembly, as sterility tests require autoinjector disassembly, making indirect CCI testing more efficient.
- The disassembly approach will be expanded to include additional brands, and more experiments using both direct and indirect CCIT methods will be performed on existing brands to enrich the library.

References

1. Wuchner, K. *et al.* Industry perspective on a holistic container closure integrity approach to parenteral combination products. *Eur. J. Pharm. Biopharm.* 194, 20–35 (2024).

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