ECA Foundation
Fostering harmonisation of GMP/GDP regulations

Container Closure Integrity Testing of Medicinal Products for Parenteral Use

– Position Paper –

A document by the ECA Foundation
Version 3.0; November 2025

Table of Contents

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Container Closure Integrity Testing of Medicinal Products for Parenteral Use	
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Version	**Changes**
Version 1.0	New Document
Version 1.1	Minor editorial revision
Version 2.0	Addition: Annex 1 new requirement statement Addition: CCI during shipping/transport validation Removal: Microbiological Environmental Monitoring Addition: Supplier Monitoring of primary packaging material
Version 2.1	Chapter 4.3: Stopper height of vials specified more precisely
Version 3.0	Update on Annex 1 requirements: original Annex 1 text and respective interpretation Inclusion of prefilled syringes in chapters 3 and 3.1 Addition of chapter 3.5 CCI Verification within Stability Testing
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1 Scope

This paper aims to highlight best practice for Container Closure Integrity (CCI) testing of medicinal products for parenteral use in the pharmaceutical industry. It should be seen as addition and complementary to the monographs of the different Pharmacopoeias. CCI testing of medicinal products for parenteral use should be used in order to ensure consistent product quality with regards to closure system integrity.

Modifications from the procedures and figures proposed in this paper are possible at any time. However, following the proposed procedures and figures may lead to safer CCI processes and may avoid discussions in GMP audits and inspections, as the described approach reflects current practice and has previously demonstrated its suitability for purpose during many years of industrial operation which includes referring GMP inspections.

2 Regulatory Requirements

2.1 European Commission and Annex 1

Currently, the regulatory requirements regarding CCI are stated mainly in Annex <1> of the European Commission (Rules Governing Medicinal Products in the European Union, Vol. 4, EU Guideline to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use)

CCI Requirements are summarized in section "Finishing of sterile products" in clauses 8.22, 8.23, 8.24, 8.25 and 8.28.

Conclusion/Interpretation:

1. Reference 8.22: "Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method."

   Interpretation: Thus, it is clear that objects sealed via fusion, e.g. ampoules, are required to undergo 100% CCI testing. Objects not sealed under fusion (vials and syringes) do not require a 100% CCI testing regime.

2. Reference 8.23: "Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge."

   Interpretation: With this, the integrity testing of containers other than ampoules and bags should undergo a product knowledge and risk based CCIT evaluation. Once integrity of the combination of primary packaging materials has been thoroughly proven in product validation, CCIT of routine batches may be performed by:

   - **Utilizing a justifiable frequency of CCIT e.g. after changes of the primary packaging material and/or on a regular basis, performing an evaluation of the CCIT within shelf life stability tests recommended for US products (see FDA Guidance Paper, see below).**

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- **Utilizing statistical sampling, e.g. according to special sampling plans for destructive testing from ISO 2859 (special inspection level S3 or S4), and performing CCIT of this sample by integrity test methods like dye ingress testing, vacuum decay or high voltage leak testing. Testing single units only is not recommended. However, the sample size available for quality control may be limited due to the size of the batches and other considerations, for instance in the case of biological products. In many cases, the sample size is 10-20 units.**

3. Reference 8.24: "Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life."

   Interpretation: This requirement was already present in the earlier Annex 1 version (former clause 123). For lyophilized products, manufacturers commonly target a slight negative pressure inside the containers (typically about 100–300 mbar below ambient pressure, depending on vial size/closure) to facilitate reconstitution by helping transfer the diluent into the container and with it reducing aerosolization/splash. Without this negative pressure, users/healthcare professionals may need to vent the container (e.g., with a second needle) to release pressure during diluent injection (reconstitution). Thus, this slight negative pressure can be viewed as an application aid rather than a strong vacuum. As a consequence, there is no need for a % vacuum test before release. Vacuum testing according to section 8.24 is to be applied for those containers where a considerable vacuum is required in order to maintain product characteristics other than only an application aid. However, this testing requirement would also apply for the application-aid-only-circumstance when it can be shown that reconstitution under missing vacuum would lead to a product with adulterated product characteristics.

4. Reference 8.25: "The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures)."

   Interpretation: Thus, a shipping/transport validation should include CCI samples to be tested based on a risk assessment of the potential impact of transport and shipping environment on the product characteristics, especially on the CCI.

5. Reference 8.28: "Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place."

   Interpretation: Thus, qualified automated stopper-height detection is one of the in-process controls that helps to prevent CCI failures during routine production. Note: stopper height control alone does not lead to proper detection of misplaced and/or not correctly set stoppers. There must be (further) controls in place which also detect these stopper related defects. According to 8.28, all these controls have to be in place before capping.

Summary statement

Once a validated CCI control strategy is in place, the Annex 1 expectations related to container-closure integrity are met initially. Ongoing verification via routine controls and during stability studies provides continued assurance of CCI over the entire shelf life.

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2.2 American Market and USP <1207> and FDA Guidance Paper:

The USP<1207> is a supportive, not legally binding, US Pharmacopeia informational chapter. According to this chapter, CCI testing should generally occur during the following three phases:

(1) the initial development of the product packaging system,

(2) routine manufacturing, and

(3) shelf life stability assessments.

The USP gives ideas and an overview of methods that can be used for the different drug products within different packaging systems.

In FDA's guidance for industry (*Container and closure system integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products*) is stated that the advantages of using container and closure system integrity tests in lieu of sterility tests within the stability protocol should be included for sterile products. Herein the CCI testing should be an additional method during the "in shelf-life" assessment of the product container closure system. It does not replace the sterility testing at the starting (T-zero) and final (T-final) stability program assessments.

3 Recommendation for 100% CCI within Parenteral Drug Product Production

Only containers closed by fusion and Form-Fill-Seal such as glass or plastic ampoules and bags must be tested 100% according to Annex <1>.

CCI should be seen as a concept established within the parenteral drug product production system where there is a need for a CCI method overview, considering manufacturing methods and technologies already in place for the manufacture of the product. CCI testing methods covered by already-in-place routine GMP requirements which demonstrate maintenance of sterility of the filled product, are shown in figure 1a and 1b. The CCI concept consists of several measures at the GMP level, which collectively ensure the maintenance of integrity of the packaging closure system.

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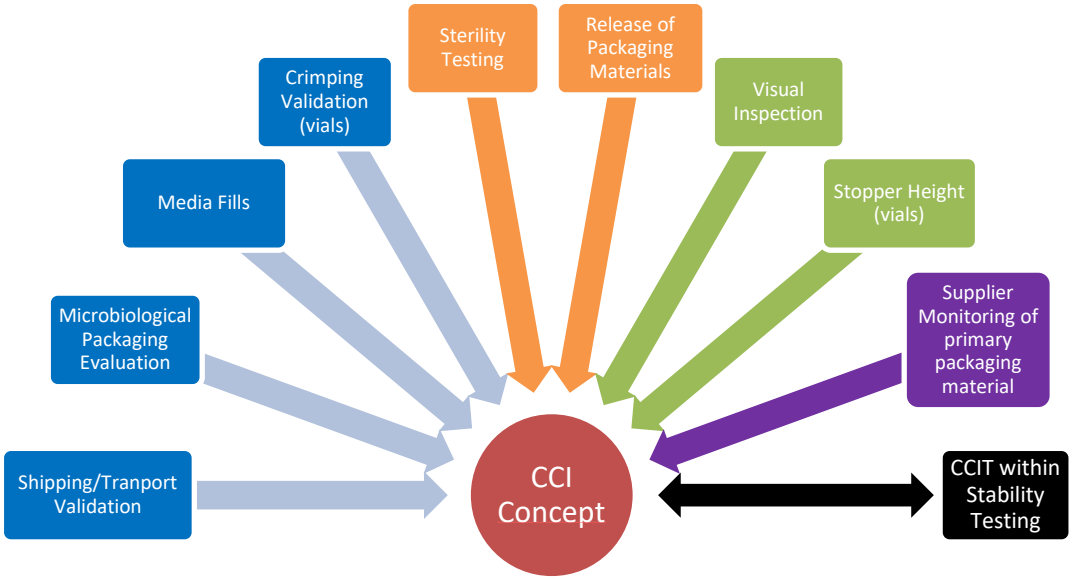

Figure 1a: CCI concept of Drug Product filled in vials

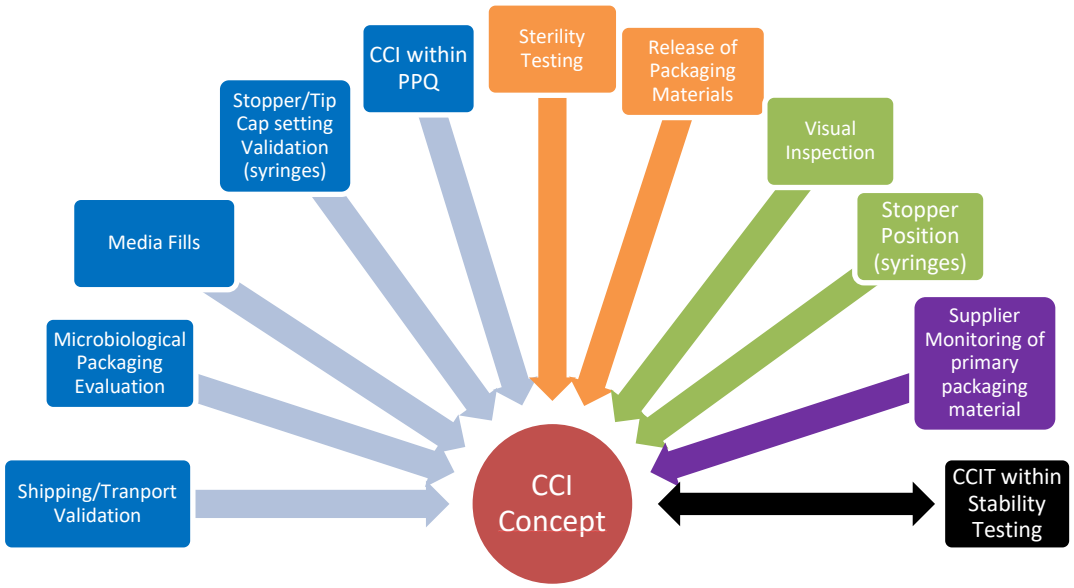

Figure 1b: CCI concept of Drug Product filled in syringes

Blue: Qualification/Validation

Orange: sampling on batch level

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Green: 100% control on batch level

Purple: Monitoring of the primary packaging material supplier on a regular basis

Black: CCI Verification within stability testing

3.1 CCI performed during Qualification/Validation (blue Figure 1a and 1b) of a Drug Product/or a Filling Line

- Shipping/Transport validation should include CCI samples to be tested.
- Microbiological Packaging Evaluation

  Evaluation of the drug product primary packaging material. Here a mCCI (Microbiological CCI) is normally performed during the development of a drug product showing that the combination of stopper/vial or stopper/tip-cap/syringe is effective as microbial barrier when subjected to the Bacterial Ingress Test (BIT).
- Media Fills (Aseptic Process Simulation)

  Media Fills show that microbiological contamination control is effective during the aseptic handling, preparation and filling of the drug product is under control from the inherent and environmental microbiological challenge (aseptic preparations). Successful (zero contaminated units) media fills (aseptic process simulations) are also demonstrating the effective CCI of filled units during manufacturing and handling of the units.
- Crimping Validation (Vials)

  The crimping validation should include CCI tests in order to show that the stopper setting and the crimping are appropriate to ensure adequate closure of the vial system (stopper, glass vial and seal). The Edge of failure CCI studies during development may be used to determine manufacturing tolerance levels.
- Syringe Requirements

  For Drug Product filled in syringes, proper placement of the stoppers has to be validated using CCI sampling within the Process Performance Qualification (PPQ). It should be performed using worst case approaches. Herein, an appropriate statistically sound CCI sample size should be applied.

  Also in regard to TipCap setting validation, processes should include CCI samples to be tested.

3.2 CCI Methods used for Batch Release on a Sampling Basis (orange Figure 1a and 1b)

- Sterility Testing

  On batch release level the sterility test performed for the batch release is also proof of correct CCI.
- Release of Packaging Materials

  The packaging materials are monitored and released prior to their use. This includes specifications for the dimensions of the syringe barrel or vial and the closing system (stopper). With this the CCI is determined.

3.3 CCI Methods used for Batch Release based on 100% Visual Inspection (orange Figure 1a and 1b)

- Visual Inspection

  The 100% visual inspection removes cracks, scratches and crimping defects. These identified defects are detected by the optical control system based on the probabilistic nature of the likelihood of a defect being present and identified. The "optical system" may be either the human eye or a camera. With this in mind, it should be considered that the detection is relative to the dimension of the defect. A purely visual inspection is not an appropriate tool by itself to monitor CCI (see referring

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section also Annex 1). This is due to the fact that the vision system cannot evaluate the robustness of the container closure relative to the microbiological challenge. Nevertheless, cracks can be detected and rejected by the visual inspection in the knowledge that visual inspection is performed on 100% of filled units prior to release of the batch.

- Stopper Height Measurement (for Vials)

  It is essential to monitor the stopper height of products filled in vials 100% during production. The validation of the stopper setting (and crimping) should include CCI tests. As an industry standard a stopper height of less than 1mm is considered to be microbiologically tight. Different heights may be validated, but the crimping validation should include a definitive CCI statement. With this the CCI is evaluated in 100% of the batch prior to the release.

All activities contributing to monitor and control CCI should be summarized and evaluated following a Quality Risk Management approach to ensure CCI is adequately and appropriately ensured - even without implementing a 100% CCI testing.

When it is determined that the risk of the summarized established detection or remediation methods do not adequately address the control of CCI of the container, then there may be the possibility of establishing a 100% CCI testing method which focusses on detecting a maximum allowable leak rate (MALR) and not merely the total integrity of the sample objects.

Note: The integrity determinations of MALR are dependent on the sensitivity of the methods used and one should take care not to create an issue by detection/testing method that does do not actually manifest itself as non-integral units in the field.

There remains the possibility to move from a 100% CCI method to a destructive CCI method using appropriate product stream sampling. If the results of the samples assessed for CCI are used for batch release, then the sampling plan should be based on a statistically appropriate sampling plan. One of the possibilities is the S-3 or S-4 level of the DIN/ISO 2859-1/ANSI/ASQ 71.4. One should take care in relying on AQL data alone for batch release. Testing single units only is not recommended. However, the sample size available for quality control may be limited due to the size of the batches and other considerations, for instance, in the case of biological products. In many cases, the sample size is 10-20 units.

As an identified CCI defect (leaking unit) it is also useful to use non-integral defect vials that are representative of normal production like real cracked vials.

3.4 Supplier Management for the primary Packaging Materials used (purple Figure 1)

The Supplier of the primary packaging material should be monitored with regard to process changes and their influence on the CCI of the drug product packaging combination.

3.5 CCI Verification within Stability Testing (back Figure 1a and 1b)

Container-closure integrity (CCI) is considered to be a lifecycle control strategy, rather than a single test. As outlined in Figures 1a and 1b, integrity at release is established by a qualified container-closure system and effective monitored process controls (e.g., stopper seating/height, crimp parameters/seal quality, visual inspection, and component/supplier controls). A validated CCIT method, applied within the routine stability program, provides ongoing evidence that CCI is maintained through shelf-life. Where a robust control strategy is in place, 100% CCIT at batch release is generally not required; assurance derives from the totality of controls plus stability CCIT (unless a risk assessment or regulatory commitment dictates otherwise).

Remark: stability study CCIT results should not be part of a release decision. When all measures shown in Figures 1a and 1b are implemented and effectively maintained, CCIT results from stability studies can be regarded as a verification step of the overall CCI concept.

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4 Recommendation for CCI Testing during the Shelf-Life Stability Assessment

For the shelf-life stability assessment, samples are taken to evaluate the CCI in parallel to the sterility assessment. The defect detection capability of the CCI testing method used should be based equal or better than microbial ingress testing. This limit can be validated using a microbiological ingress test or can be based on limits given in the literature. It may be useful to ensure this CCI after or during product development, otherwise it might lead into the detection of CCI defects of non-realistic/non-production representative defects.

When investigating identified CCI defects (leaking units), it is also useful to use non-integral defect vials that are representative of normal production like real cracked vials.

5 References

- EU GMP Annex 1, Rules Governing Medicinal Products in the European Union, Vol. 4, EU Guideline to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use), 2022
- USP <1207>
- FDA Guidance Paper for Industry: Container and closure system integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products, February 2008

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