in 2008 with the publication of an updated document [24]. The wording in [24] is as follows: “The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.” And also “Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.” “Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100 % integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures” and “Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.”

This ruling, as well as the 2004 Food and drug Administration (FDA) Guidance on Aseptic Processing [25] that contains statements pointing in the same direction, have spurred many pharmaceutical companies to look more critically at the condition of their freeze-dried products between stoppering and crimping, e.g., [26] that illustrates a 100 % camera control of stopper placement before capping and the rejection of vials with stoppers that have excessively raised, based on results of helium leak rate testing.

The increased attention for CCI for a part has coincided with the advent and acceptance of novel nondestructive inspection techniques. Among the latter, laser-based headspace analysis is in a very prominent position for freeze-dried vials. It is a technique based on laser absorption spectroscopy that is suitable for measuring gas concentrations and vacuum levels in the headspace of vials in a nondestructive manner. When the same vials are measured over time, changes in gas concentrations, also if they are temporary, can be detected on the finished vial after crimping. The technique is extensively discussed in [27–28]. It is meanwhile offered by various companies. References of the most cited providers can be found in [29, 30]. The fact that CCI for lyophilized vials is not a given thing, and that it may vary from batch to batch, is illustrated in [31], where the investigation of in total nearly 14.6 million lyophilization vials revealed an average CCI failure rate of 0.67 % with serious outliers in particular batches.

A factor that may even put more focus on CCI is the revision process for United States Pharmacopeia (USP) <1207>, “Sterile Product Packaging—Integrity Evaluation” [32] that is going on at the time of writing this chapter. So far, in terms of CCI evaluation for sterile products, mostly USP <1207> and Parenteral Drug Association (PDA) Technical Report (TR) 27, “Parenteral Packaging Integrity” [33], were the two most cited documents. In future that will probably remain the case, however, as a result of the revision process in which both documents are in, their relative significance is going to change. At present USP <1207> [32] describes integrity testing as a pharmaceutical product package life cycle testing activity, starting at product package development and later on covering the stages of routine manufacturing testing and marketed product stability testing. It mentions physical tests and microbial challenge tests, but it does not go into details. An extensive listing of testing methods as well as more details on them can be found in PDA TR 27 [33]. The revision process of both documents has not been concluded yet, but from what has been publicly presented so far, it may be inferred that some significant changes are