Technologie / Lyophilisation

Developments in Container Closure Integrity Testing of Lyophilised Product

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Container closure integrity plays an important role in maintaining the sterility and stability of sterile lyophilised products. Defects which cause a freeze dried vial to leak are not necessarily detected by a visual inspection process. Examples of such defects are microscopic cracks & scratches in the glass, defects that are hidden by the crimp, or temporary defects such as stopper pop-up that result in temporary container leakage. Increasingly, 100% automated container closure integrity testing (CCIT) is being implemented to complement visual inspection for controlling the quality of finished sterile vial products.

It has been communicated that the EU GMP Guidelines for the Manufacture of Sterile Medicinal Products Annex 1 will undergo a revision [1]. One of the revision topics is the container closure integrity (CCI) inspection of sterile product. In recent years, this has been and continues to remain a hot topic. Current EU Annex 1 regulations require 100% integrity testing of containers closed by fusion (i.e. ampoules) due to the inherent risk in these sealing processes. The requirements for other containers are vague and it is expected that revisions will address this issue.

Another regulatory development in this area is the release for public comment of a revised version of the USP <1207> chapter on container closure integrity [2]. This revised chapter is scheduled for implementation in 2016 and promises to stimulate some significant changes to practices in this area. One of the points in the revised <1207> chapter is the identification of CCIT methods as being probabilistic or deterministic. Traditional CCIT methods such as microbial challenge tests or blue dye ingress tests are described as methods associated with probabilistic outcomes that result in some uncertainty in findings as well as in difficulties to quantitatively validate the method for the detection of critical leaks. Other CCIT methods that are based on analytical measurements, such as helium leak testing, laser-based gas headspace analysis, or vacuum decay, are described as methods that produce objective, quantitative data that enables the detection of critical leaks as well as analytically based validation.

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These deterministic CCIT methods coupled with a risk-based approach can be used to generate statistical CCI data that enables informed decisions about implementing a container closure integrity inspection process. A recent White Paper from the BioPhorum Operations Group, a collaborative working group of the industry's leading biopharmaceutical companies, outlines a rational and risk-based approach for when and how to apply 100% CCIT [3]. The White Paper also highlights when other approaches, such as process control and in-process testing might be more applicable.

For the specific case of sterile freeze dried product, generating CCI data to obtain a statistically relevant understanding of the vial sealing process quality in production is key when using this approach. Recently, CCI benchmarking data from more than 15 million commercial freeze dried product vials that were produced over a five year period at five different global facilities has been analysed and presented [4]. The data shows that the freeze drying process introduces risk to the seal integrity of a freeze dried product vial due to the complexity of the sealing process as compared to the liquid filling process. The CCI benchmarking data showed that it is not unusual for up to 0.5% of commercial freeze dried product to suffer from leakage. In the data analysed, more than 80% of the commercial lyo batches contained at least one leaker vial. Some of these leaks were temporary with the data analysis indicating that the vial was leaking between the lyo chamber and the capping and crimping machine. During this temporary leakage, the freeze dried vials lost their (partial) vacuum and ingressed oxygen resulting in loss of the initial nitrogen headspace.

Generating statistical CCI data might seem like a challenging task. However, a number of automated leak detection platforms are readily available that can be implemented and validated to perform statistical CCI studies. This can be especially interesting for performing process studies on placebo test batches and validation batches produced during scale up and product launch, or for inspecting batches with suspected CCI issues to enable release of the product to the market. Processes which are shown to pose risk to vial seal integrity may require 100% CCI inspection as part of the commercial production and packaging process [3].

In summary, recent industry developments in the area of container closure integrity of sterile product again means that this topic will remain an important one in the coming year. The use of deterministic CCIT methods for validating closure of packaging components, and the implementation of 100% CCI inspection for lyophilised product are two trends to look out for in the near future.

Résumé

Le container closure integrity joue un rôle important dans le maintien de la stérilité et de la stabilité des produits stériles lyophilisés.

Les causes pouvant occasionner un défaut d'intégrité ne sont pas forcément détectables lors d'une opération de mirage. Quelques exemples classiques: micro-fissures et rayures d'un contenant en verre, défauts masqués par l'opération de sertissage, ou défauts temporaires de type bouchon mal enfoncé qui conduisent à une fuite temporaire du contenant. L'industrie pharmaceutique et les organismes réglementaires sont aujourd'hui d'accord sur ce point. Le container closure intégrité (CCI) est également d'actualité dans les dernières évolutions réglementaires, telle que la révision de l'annexe 1 des Bonnes Pratiques de Fabrication de l'union européenne, ou celle du chapitre de l'USP <1207> sur ce sujet. La révision de ce chapitre de l'USP <1207> introduit une distinction entre les méthodes probabilistes utilisées comme test d'intégrité (bleu de méthylène, challenge-test) et les méthodes déterministes (test à l'hélium, mesure laser du headspace, dépression). Les méthodes déterministes donnent des résultats analytiques objectifs, et peuvent être utilisées pour valider de manière quantitative la détection de fuites critiques. L'industrie pharmaceutique a commencé à générer des données statistiques permettant d'identifier les process à risque pour l'intégrité des produits. De plus en plus, des solutions automatisées de contrôles à 100% sont mises en oeuvre en complément du mirage pour maîtriser la qualité des médicaments stériles.

Bibliographie :

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