

Out in the Cold

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Various obstacles make it challenging to implement PAT Guidelines in lyophilisation; Thomas A Jennings at Phase Technologies, Inc outlines the solutions

Thomas A Jennings, PhD, is an expert in vacuum technology and lyophilisation. Thomas has focused on lyophilisation for about 30 years, having worked for several years for one of the largest manufacturers of freeze-drying equipment before founding his own company in 1978. In 1990, he formed a new organisation, Phase Technologies, Inc, with the vision of transforming lyophilisation from an art to a science. Thomas holds a PhD in Physical Chemistry from the University of Aston, Birmingham, England and a BA and MA in Chemistry from Temple University. He has been awarded

numerous patents and has recently filed two patent applications with the US Patent Office involving new technology for determining the moisture content in dried products and elastomer materials. He is the author of numerous technical publications involving the lyophilisation process and freeze-drying equipment and instrumentation. At present, he is serving a three-year term as President of the International Society of Lyophilisation – Freeze Drying, Inc.

While the Process Analytical Technology (PAT) Guidelines are revolutionary and welcome to pharmaceutical manufacturers, nonetheless, PAT really has its foundation in the concept of Six Sigma, which has been used with great success in the electronics industry for years. The term sigma refers to standard deviation, which is how far a measured value varies from the mean or the desired value. The underlying philosophy of Six Sigma is that the manufacturing process is so well controlled that the number of defects would only amount to 3.4 parts per million (ppm). However, if one uses a Three Sigma approach to production, then the output would be 99.73 per cent, translating into defects or failures in the order of 2,700ppm. Once a pharmaceutical company demonstrates its manufacturing process has achieved the Six Sigma goal, then the real-time release of manufactured pharmaceutical products will no longer be hypothetical but will become a reality.

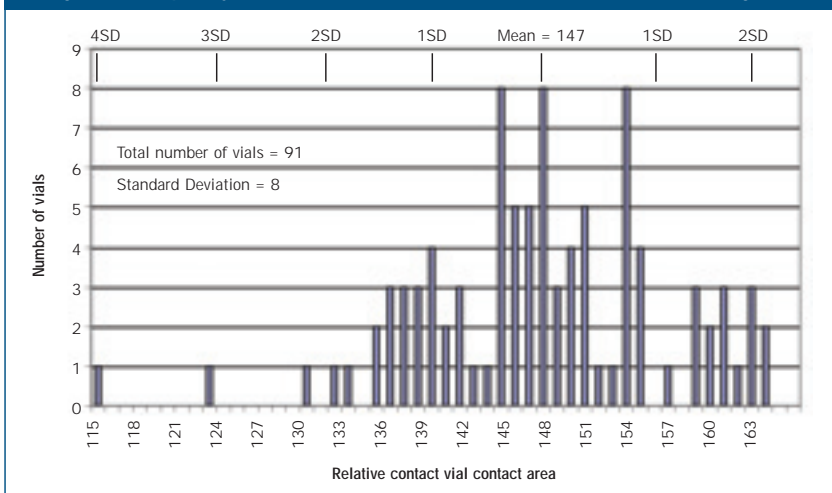
There is no doubt that achieving real-time release of a pharmaceutical product will be a challenge for any manufacturer, but if the final step in the manufacturing procedure requires the use of the lyophilisation process, then meeting the PAT Guidelines becomes an even more formidable task.

One of the fundamental obstacles facing the lyophilisation process is that it began as an art form and, in spite of efforts by many to add science to this technology, the idea that lyophilisation is an art still persists throughout the pharmaceutical industry. As a result, there is resistance to the implementation of major change to a process that has been used for years, and for which the output of a production batch may only be 90 per cent. Therefore in the present climate there is little hope of achieving process control that would even meet Three Sigma, so achieving Six Sigma becomes unthinkable. Thus, the first task for any pharmaceutical company that uses the lyophilisation process to manufacture a product would be to insist on basing lyophilisation on science and not art. Art and PAT are simply not compatible.

A pharmaceutical manufacturer that wishes to introduce science into the lyophilisation process must deal with many issues. Let us first assume that the formulation will not vary from batch to batch and just consider an inherent effect that nature has built into the lyophilisation process and that, for the most part, we have chosen to ignore up to this point.

During the freezing process, a frozen matrix will be formed comprising of ice crystals and an interstitial region consisting, for all except a few products, of a glassy system. In order to prevent collapse or meltback of the lyophilised cake, we must establish the collapse or phase transition temperature. Determining the collapse temperature can be a time consuming process and the data are not easy to interpret, so it is often the case that only one measurement is made. However, because the composition in the glassy interstitial region does not have a stoichiometry composition, the make-up of the interstitial region will vary from vial to vial. Hence, we are dealing not with a single collapse temperature but a frequency distribution

Figure 1: Frequency distribution of the relative contact area of 10ml tubing vials



of collapse temperatures. Since vials with the lowest collapse temperature cannot be eliminated from the batch, one must base the freezing and drying process on a product temperature that is significantly lower than the mean. As a result, the freezing process may have to be extended and one could be faced with an extended primary drying process. While we will need new instrumentation that would permit the rapid determination of the frequency distribution of collapse temperature, the real answer lies in obtaining a formulation that has a frequency with a relatively high mean collapse temperature and standard deviation of the order of tenths of a degree Celsius. Only then can we safely use the mean collapse temperature in determining the operating parameters of the lyophilisation process.

Considering now the primary drying process, energy is needed for the sublimation of the ice. This energy is generally supplied by thermal conductivity between the shelf surface and the contact area of the container, and the heat transfer from thermal conductivity of the gases between the bottom of the container and the shelf surface. For the purposes of this discussion we will assume that the container is a glass tubing vial.

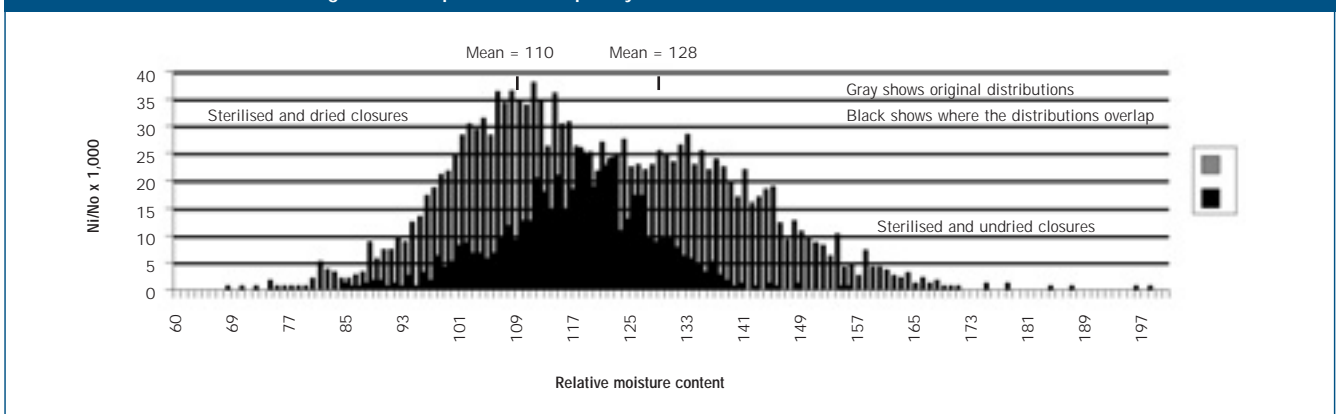
Now, assuming that we have an ideal dryer where there is no variation in shelf surface temperature across the shelf or from shelf to shelf, and that pressure is uniform throughout the dryer, one would be inclined to believe that the sublimation rate from each of the vials would be similar. Unfortunately that is not the

case as shown in Figure 1, which shows that there exists a frequency distribution for the surface contact area of the vials. Thus, in spite of the presence of a uniform shelf surface temperature in the dryer, the amount of energy transferred can vary from vial to vial as a result of the variation in the surface contact area of the vials. Those vials with an unusually high surface contact area will receive more energy and, although the sublimation of ice may occur at a higher rate, there also exists the possibility that the product temperature may exceed the collapse temperature and lead to collapse or meltback of the final product. For those vials that deviate from the mean with a low surface

contact area, the sublimation rate will be lower and result in a defective cake with partial meltback. The manufacturer is now faced with the choice of either lowering the sublimation rate of the ice and extending the primary drying process to compensate for those vials that have a low contact area, or removing these vials before they reach the filling process.

Determining the end of the secondary drying phase has always been something of a dilemma. Here again the contact area of the vials can be an important factor. Even if the problem with the contact area of the vials is resolved, one still faces the problem of when to terminate the drying process. Even if a few vials from the front of a shelf are removed and measured, the number is not significant statistically. Usual methods for determining residual moisture in the cake remains either loss-on-drying or the Karl Fischer method. Both are destructive in nature and destroying large numbers of good product to assess the product is economically unacceptable and not in keeping with the spirit of the PAT Guidelines, where quality is not tested into the product but built into the process. So the industry is faced with the challenge of finding a non-destructive means that will first allow us to achieve Three Sigma confidence that the product has completed the secondary drying process, while still in the freeze dryer. Should that technology become available then perhaps there is hope of being able to say we have a lyophilisation process that will meet the Six Sigma goal.

Figure 2: Comparison of frequency for sterilised dried and un-dried closures



When we have the technology to build quality into the lyophilisation process so as to meet PAT Guidelines, we may erroneously arrive at the conclusion that our task has been completed as soon as the product leaves the manufacturing plant. The PAT Guidelines for a product extend beyond the point at which we have achieved real-time release and must also include the moment that the product is administered to a patient. Is the quality of the product when it is administered to the patient the same as when it was released for shipment? Has the moisture in the product been reduced because of the selection of an excipient like lactose that will convert to a monohydrate? A significant reduction in the residual moisture in the product can lead to a loss in activity of a protein product. Or has the residual moisture in the product risen above its acceptable limit as a result of outgassing of water vapour from the closure? While both instances are possible, the latter is much more likely.

Depending on the cake's mass, outgassing of moisture from the elastomer closure can represent a potential risk to the stability, and hence a reduction in quality of the lyophilised product. Thus the quality of the product received by the patient can differ from that which left the manufacturing facility. For lyophilised cakes with masses significantly greater than 100mg the risk of loss in quality as a result of outgassing water vapour from the closure will be minimal. But for product cakes with a mass of less than 100mg, the risk of a change in the quality of the product is real and should not be ignored, as the threat of an increase in residual moisture will increase as the mass of the cake decreases. Thus, for lyophilised

cakes with a low mass, it is imperative that the moisture content in every closure be known to contain insufficient moisture to affect the quality of the product during transit.

It has been shown that, depending on their composition, closures can contain a significant amount of moisture even as they are received from the manufacturer. The steam sterilisation process will only increase the amount of moisture absorbed by the closures. The closures are then dried to reduce moisture to a safe level. However, most closures used in the production of lyophilised cakes are sterilised and dried in special bags. Figure 2 shows the frequency distribution of the relative moisture in a bag of closures after steam sterilisation, compared to the frequency distribution in a bag of closures after steam sterilisation and drying. Note that from the frequency distribution of the dried closures some have the same relative moisture as that of the closures after steam sterilisation. The question is, do such closures pose a risk to the quality of a lyophilised product?

These are just a few of the challenges that face those seeking the holy grail of Six Sigma in their lyophilised process. Time will tell if the pharmaceutical industry will rise to meet these challenges or merely pay lip service to PAT and continue to do what they have done for many decades. ♦

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