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Cyclic Temperature Stress Testing of Pharmaceuticals

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In a previous communication the present authors have commented on some aspects of stability testing (1). The objective of the present brief paper is to comment on the design and application of cyclic temperature stress testing for pharmaceuticals. We believe it to be timely to offer such comments now because of the present increased interest in this topic and because at present there is considerable variance in the design of such tests. It is our contention that there are some aspects of the design of cyclic temperature stress tests which could now, with considerable advantage to all concerned, be standardized and others which must be adjusted to meet the specific needs of individual drug products. The purpose of this communication is to distinguish between these two types of attribute.

Firstly, it is our belief that there are powerful arguments in favor of standardizing the period of the cycle (i.e. the time which elapses from maximum temperature through the minimum and back to maximum) as twenty-four hours since the diurnal rhythm on Earth is twenty-four hours and thus marketed pharmaceutical products are most likely to experience such a cycle during storage. We submit that cycle temperature stress tests should be designed, whenever possible, to mimic likely conditions in market place storage.

For similar reasons we believe that the equation relating temperature change to time should be a sine wave since, on average, this is the normal way in which temperatures change in non-environmental controlled situations. Equipment allowing temperature to change in this manner is commercially available in both North America and Europe. We are aware that in some facilities lack of suitable equipment has mandated the use of square wave or rounded square wave type equations and we appreciate that it can be argued that a square wave type program is likely to more stressful - in some regards at least -

than is a sine wave program. However, we believe that coincidence with natural storage conditions is more important than increasing stress.

There has been, and likely will probably continue to be, lively discussion about the maximum and minimum temperatures within which the products should be cycled. We propose that for climate zones one and two reasonable maximum and minimum temperatures for many products are 40° c and 4° c, since data from stored products suggests that it is very rare for warehouse temperatures to exceed 40° c in climate zones one and two. We are aware that some workers in the field of stability testing recommend a maximum temperature of 45° c and we concur that this may well be appropriate for climate zones three and four but represent a cruel and unusual punishment for products which will only be distributed in zones one or two. Obviously, if a product can tolerate freezing there are arguments in favor of a minimum temperature below 0° c. We submit that the choice of maximum and minimum temperatures must be decided on a product by product basis and take into account such factors as recommended storage temperatures for the product and specific chemical and physical degradation properties. A special case where quite atypical maximum and minimum temperatures are obviously justified is in freeze-thaw cycling of aqueous solutions of protein drugs where temperatures of +8° c to -5° c are commonly used. This test is somewhat specialized as it is normally performed specifically to evaluate aggregation problems.

One question often raised concerning temperature stress testing of pharmaceuticals is how long should such tests be performed. We know of no theoretical basis for calculating the answer to this question. However, based on experience in our own laboratories and data which has been made available to us as consultants, it is our view that a test of about twenty cycles is probably as effective in revealing problems as any. Indeed, in many instances problems become evident within ten cycles.

There appears to be some feeling in the industry that cyclic temperature stress testing is mainly, if not exclusively, of value for liquid pharmaceuticals. Certainly, we agree that for products such as emulsions cyclic temperature stress testing can be especially useful. However even for tablets packed in plastic bottles such problems as cap loosening, loss of label adhesion or migration of plasticizer into the label causing the ink to run may sometimes be more clearly evident from cyclic rather than isothermal tests. Even blister packed tablets can in some instances show surface blotching (caused by water vapor condensation) which would not be observed on isothermal testing.

It is our belief that cyclic temperature stress testing is a very useful component in the gamut of tests available to the pharmaceutical scientist (2,3) for stability testing. We hope that whenever possible the nature of such tests will be, as indicated in this communication, standardized to improve ease of interpretation.

References

1. Drug Development and Industrial Pharmacy 14 1785-1790 (1988) J. T. Carstensen and C. T. Rhodes.

2. Modern Pharmaceutics, Second Edition, Edited by G. S. Banker and C. T. Rhodes, Marcel Dekker, Inc. NY (1989).

3. Drug Stability, Jens T. Carstensen, Marcel Dekker, Inc, NY (1990).