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MARKET STRESS TESTS

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14.1 Introduction

The pharmaceutical scientist faced by the task of assigning an expiration (or salary expiry date) to a product is likely to use more than one source of data in order to reach a rational and informed judgement. Accelerated stability tests and other formulation and preformulation laboratory studies can indeed be useful, so can consideration of published data concerning similar products. Also, of value can be a consideration of retained and returned sample data. Additionally data obtained from test market distribution studies or laboratory "market stress" tests can play a role in the process of defining product stability.

14.2 Market Stress

Typically, a finished pharmaceutical product once it has been given market release approval by a quality control and assurance unit, will be stored for some time in the manufacturer's warehouse before being transported first to the wholesaler's warehouse and then to the community or hospital pharmacy before being provided to the patient. This process, which can of course, have many variations, is often characterized by the manufacturer having an increasingly reduced level of control as the product moves further along the

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channels of distribution. This is particularly likely to be true if international marketing is involved. Thus, while the manufacturer should certainly be able to count on the product being appropriately stored at the production site there may well be legitimate grounds for concern about the stress to which the product will be subjected before it is finally used by the patient. Certainly, it is to be hoped that the wholesaler and hospital or community pharmacist will treat the storage and rotation of stock in a professional manner. However, even when this hope is justified, the transport process can impose considerable stress on the product. It is now recognized by many concerned with the stability of pharmaceuticals that the conditions of storage of pharmaceutical products by the user is often a major cause for concern.

Although it would surely be unreasonable to expect the manufacturer to be legally responsible for the conditions of storage of pharmaceutical products by individual users, there is certainly reason for manufacturers and others to do all they can to educate the public about the importance of the appropriate storage and use of drugs. Community and hospital pharmacists can play an important role in this process.

Market stress imposed on a product can take a variety of forms: high temperatures, low temperature, temperature change, humidity, load, impact, abrasion, light and biological aspects are among the factors which may be relevant. Often, the combination of two or more of the above factors has a particularly harmful effect. Thus, storage at conditions of high temperature and high humidity is, for many products, an especially vicious combination, which can have serious adverse effects on stability.

14.3 Temperature Data

Of all the environmental factors which can adversely affect the stability of pharmaceutical products, temperature, and temperature change, are often given special attention. As has been pointed out in chapter one, there is good reason for this, since, of all the environmental factors which can accelerate degradation, temperature is the one which can not be controlled by package selection.

There is, therefore, considerable interest in obtaining information on climatic conditions in the area where any given product will be marketed. If a product is being marketed in a temperate zone, where air conditioned, warehouses are used and distribution is rapid so that, for example, 95% of a given batch is used within two years, (i.e., T95 < 2 years), climatic data may not be critical. However, when a product is exported to areas where climatic conditions are extreme and warehouse design and use are somewhat rudimentary and distribution is slow so that the T95 exceeds four years, climatic data is of grave importance. One of the most reliable and comprehensive sources of climatic data is the six volume "Tables of Temperature and Relative Humidity and Precipitation for the World" published for the Meterological Office in London by Her Majesty's Stationery Office.

14.4 Warehouse Design and Distribution Control

Even in areas of the world where material supplies are scarce, a relatively simple warehouse design, if used with appropriate stock rotation, can provide an adequate degree of protection for most pharmaceutical products. Keeny, Rhodes and Schearer in "The Purchase, Shipment, Storage and Distribution of Contraceptives in Developing Countries", a book produced under contract for the World Bank, have described, in some detail, the design of an inexpensive model warehouse which could be used in many areas of the world. They have also directed attention to the importance of regulating the stress which products may be subjected to during distribution.

This topic is attracting considerable interest from a number of pharmaceutical and international agencies involved in the purchase distribution and use of drugs. Some companies, having investigated the problems of distribution in tropical areas of the world, have decided that it is necessary to introduce a special heavy duty pack. It is understood that at the time of completion of this chapter (Spring 1984), the U.S. Army is giving special attention to the problems of storage of drugs throughout the world. The Army has very substantial sums invested in drug products. Also, as a result of investigations of distribution and storage problems in certain countries, some companies and agencies are introducing training schemes for those in-

volved in such activities. Even just application of basic storage principles, such as "First In - First Out", have in some instances had a dramatic effect in reducing stability problems.

14.5 Market Stress Tests

How well do our products stand up to stability stress imposed during distribution? This question, although difficult to answer, is one which justifies considerable attention. A number of different approaches can be used in order to obtain information on this topic.

Analysis of both retained and returned samples can provide useful insight into stability. Retained samples will, presumably, be stored exactly as the manufacturer recommends and thus are likely to give an orderly optimistic view of the product's likely condition after having been exposed to market stress.

Most manufacturers from time to time, have unsold products returned to them from wholesalers or retailers. There is no generally accepted procedure for dealing with such materials. Whatever else may be done with them, a strong case can be made for a comprehensive analysis of some samples of returned product. It is the author's experience that returned product analysis will often tend to give an unduly pessimistic view of stability. This is probably because returned product is not a random sample representing an average product, but a representation of the slow moving "tail" of the product. My experiences has been that low sales outlets often store products in a less well-controlled manner than average.

Test distribution of product is used by some manufacturers to provide evidence of the ability of a product to resist market stress. The numbers of samples tested and the mode of testing vary. In general, however, samples are sent through the normal channel of distribution to the retailer who is instructed to return the samples to the manufacturer. Tests on these samples are often focused primarily on the package and label. Obviously, such tests are by no means infallible indicators of product robustners and resistance to market stress. During test distribution, the transport carton may never

be dropped, whereas once full scale distribution is started dropping transport cartons may occur, and cause damage to product, with a depressingly high frequency. Also, it must be kept in mind that test distribution at different times of the year may impose significantly different thermal stress on the product. Products shipped in January may be left on a loading dock at 5°F while in July the temperature on the dock may be 95°F. However, when taken in conjunction with other data, results of test distribution can provide useful information on product stability.

During recent years a number of industrial and academic pharmaceutical scientists have given considerable attention to developing laboratory tests, which will mimic market stress. Considerable ingenuity has been demonstrated in the design of such tests, unfortunately there is not a generally accepted method and indeed still much lively debate on this topic.

It is relatively common to use cyclic temperature stress tests in stability programs. The usual cycle is of 24 hours duration and as it corresponds to diurnal rhythm, it seems to this author to be a logical choice. However, some workers use a weekly cycle. If in our cycling test it is our interest to reproduce storage temperature in a warehouse, there is a good reason to use a sine wave program to control the variation of temperature as a function of time. Some groups use a temperature:time system in which, virtually, a pure sine wave is used. Others, either from choice or because of equipment limitations, use a square wave system, in which the temperature between the two extremes of the cycle is changed very rapidly. It is argued by some that such a change provides a more rigorous challenge to a product.

A matter of lively debate is the selection of the limit temperatures between which the product is cycled. Perhaps there is a need for more than one temperature range, depending on the product and the market for which it is intended. It is this author's opinion that 40°C is a reasonable choice as the upper limit for a product to be marketed in the United States, since the confined room (non-air conditioned) storage temperature rarely exceed this value for any lengthy period of time. (The confined storage room temperature maximum is normally several degrees lower than outdoors maximum: also, whereas

the outdoors maximum may be reached at, say 3:00 P.M. the confined room storage temperature maximum is likely to be several hours later, at perhaps 7:00 P.M.). Other workers prefer to use 37°C or 45°C as the upper limit of the cycle.

For the lower limit temperature, the author commonly uses 4°C. Other workers use 0°C or -5°C. However, it must be kept in mind that some products, such as many emulsions, can not tolerate freezing and for such systems any freezing temperature could well be regarded as an excessive stress.

How long should a cyclic stress test be operated? Again, there does not appear to be any consensus. The author is aware of different groups which use one week, one month or two months.

Some groups like to use cycle stress tests, which impose a combination of humidity and temperature stress tests on their products. Also, there are groups which have devised special stress tests for products designed for distribution in tropical areas. Unfortunately, the detailed procedures used by many groups are regarded as confidential and are not published. The rationale here is not obvious.

Samples subjected to temperature cycling tests are carefully evaluated chemically, physically, and microbiologically with respect to both product and pack. Chemical tests for the amount of active, and also perhaps degradation products and other components such as preservatives, can be made. Physical tests can include such techniques as tablet hardness, redispersability of a suspension or color of a solution. Microbiological tests can include both total viable count and tests for specific organisms as well as quantification of preservative capacity.

In evaluating samples subjected to market stress tests, it is often very useful to give special attention to the package. The appearance, when evaluated in a systematic manner by an experienced person, can be of considerable value. Is label adhesion still satisfactory? Is the color of the label and clarity of the printing still acceptable? Is the back-off torque of any cap still within limits? These are among the questions which may be usefully asked.

The tests applied for any given product should be clearly related to the properties of that product. Sometimes a degree of overkill is present in testing. Sophisticated instrumentation is not always necessary. For example, a simple pourability test for an emulsion may be quite satisfactory for many purposes: a routine evaluation of complete rheological properties using a recording ciscometor, such as a Ferranti-Shirley, may well be unnecessary.

14.6 Summary

Market stress tests can be of considerable value to the pharmaceutical scientist investigating the stability of doing products. Unfortunately, at present there is not clear general agreement on the tests to be used in such studies. There is a strong case to be made for a professional group attempting to develop standardized tests in this area. As a first step to reaching a consensus on what tests to use, pharmaceutical scientists should be actively encouraged to publish their ideas on this topic. At present the literature has a paucity of papers on this topic.