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RATIONAL STORAGE TIME POLICY IN PRE-NDA STABILITY PROGRAMS

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On the surface, it should be rather simple to carry out a stability program at room temperature during the development of a drug. Batches used for this purpose are either experimental batches, batches for toxicology or clinical batches. They are manufactured, a sample is taken, this is placed at the room temperature station, and samples are removed at the protocol times, e.g. after 3, 6, 9, 12, 18, 24 and 36 months.

It is never known, at an early point in time, whether the product will ever reach the NDA-stage, but batches are always placed on stability with this (desirable) possibility in mind. If the NDA stage is reached, then such batches often constitute a

substantial portion of the stability profile which the FDA evaluates in their approval of a temporary expiration period.

From a practical point of view, however, the picture is not quite as simple. There is, first of all, always a possibility of a batch not being placed on stability shortly after it is manufactured. This may be due to man-power overloads either in the sampling or the stability section. This pre-lag time is denoted *t'* in the following.

If a batch, hence, is stored at room temperature for *t* months, then it has, at this point actually an age at room temperature of [t+t']. *t'* is frequently (but not always) small. More serious is the lag time which may occur between the so-called "pull time", i.e. the time when the sample is removed from the room temperature stability station, until the time it is assayed.

Assays of this nature are frequently carried out by an analytical section that is associated with Research, i.e. not the usually analytical arm of Quality Control. This Analytical Research section most often is in charge of Methods Development, and is frequently overloaded. Samples submitted for assay may, therefore, be kept for a certain length of time, the post-lag time, *t"*, until assayed, so that the *real time* storage period at room temperature is [t+t'+t"].

It may be difficult to carry out a stability assessment of the data if *t'* or *t"* are of substantial magnitude. If the assay is a 3 months assay and the sum of pre and post lags is also 3 months,

then there is, of course a 100% error on the time point. Lines are evaluated by least squares fitting methods that assume that the time axis is not afflicted with error[1], hence statistical treatment in such a case would actually be incorrect.

It might be argued that by reporting a figure as being stored at 3 months, whereas it had indeed been stored at 6 months, one is biasing the data to one's own disfavor. But this is not entirely true, because if there is an initial loss (oxidation[2], limited moisture[3,4]), then this fall-off may well be masked, and simply show up as a low initial assay. This would distort the stability picture, particularly if the assays were reported as percent of initial.

The correct solution to the stated problem would, of course, be to have a heavily, if not over-staffed analytical group. This is not a practical solution, and a better solution might be to report the actual times of storage, i.e. t+t'+t". This has two disadvantages. One is that the final protocol will differ from the one originally suggested. The second is that it makes tabulation exceedingly clumsy since it would only be accidental that any two storage times would be identical (because t" would be different in each case). Finally, it suffers from the fact that room temperature was rigorously controlled for a period of *t* months and only approximately controlled for *t'+t"* months. This latter point is probably not that serious, since the temperatures in analytical and storage areas are fairly well controlled in most industrial situations.

A better way of handling the situation was proposed 7 years ago[5]: it was suggested to freeze (-5 to -15°C) solid dosage form samples during the pre-lag and post-lag times, so that the storage time at room temperature would be *t*, i.e. the intended storage time. To imply, in a stability table, that the pre-lag and post-lag times, i.e. the time spent at freezer temperature, were e.g. 2 months, can be done simply by writing (2) (i.e. 2 in parenthesis) after the assay, and indicating in the table that this is the convention used.

One or two samples should be kept in the freezer for the length of the expiration period to substantiate that there was no loss sustained during this period.

One exception holds for the above, viz. stability samples for dissolution. Freezing a sample may well alter a dissolution profile, and the procedure is therefore not recommended for this test.

The method has other advantages. In early development, the assay is not always perfect, and if an improvement is introduced, say 8 months into the program, then the dilemma exists that original data (e.g. accelerated data) were generated with the "wrong" assay. If duplicate samples of initial, room temperature, and accelerated samples are kept at freezer temperatures, then the stability profile can be duplicated with the new assay.

Frequently the point in time an assay is performed attributes to the variance of the points on a stability line. The time-of-assay variance implies that if e.g. a completely stable sample were assayed after 3, 6 and 12 months, different assays would result due

to the fact that they were assayed at different times (i.e. the variance would differ from that obtained by assaying on the same day). Freezing an initial sample can be of advantage in the analysis of such a situation as well. Freezing would allow an "initial" to be assayed at the same day as a sample stored for 6 months at room temperature, hence eliminating the time-of-assay effect. It should be noticed that this does not differ from the biopharmaceutically accepted practice for blood level samples. Here all samples are drawn and frozen, and all assayed at one particular time.

The above procedure might also be practical with liquids, except here refrigerator storage would be resorted to. In such a case a stability study at $4^{o}C$ (albeit with only a few points) would be necessary to establish that the cool storage was tantamount to "no loss".

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