

The containers are assessed as well, but in this respect the effect of oxygen and moisture, as covered in the next chapter, are probably more à propos.

The containers to be used in the long term, real time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution (116–118).

The 1993 ICH Guidelines address the evaluation of data as well. It is noted here that it is necessary to attempt to establish the “degradation relationship”, i.e., attempt to assess the mechanism of degradation:

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve (138–143).

There is the admission of limited extrapolation of data, but here again, it is necessary to know the degradation pattern:

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data etc. (149–155).

The guidelines again emphasize the need for assessment of degradation products and “appropriate attributes”:

Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes (156–157).

Such “appropriate attributes” are most commonly, for a bulk drug substance, morphology, particle size, shape, and fractal dimension.

1. SIMPLEST DECOMPOSITION MODES OF PURE SOLIDS

If a solid is placed in a vacuum and exposed to temperatures at which it decomposes at a measurable rate, one of the following situations may arise:

- I Solid → solid + solid
- II Solid → solid + liquid
- III Solid → liquid + liquid
- IV Solid → solid + gas
- V Solid → liquid + gas
- VI Solid → gas + gas

Other schemes are theoretically possible, but not likely. Of the above, it is schemes IV and V which will be treated in some detail below, because they are the ones most investigated in the pharmaceutical sciences. It will later be shown that most pharmaceutical systems will not be of such a purist nature, but the experiences gathered from examining them will throw light on several important real-life situations.