



Figure 1 Least squares regression analysis.

statistical methods to calculate the 90% confidence zone of the regression line. This means that there is a 90% probability that the true regression line (of label claim potency as a function of time) is within the zone. Thus there is only a 5% chance that the true line is really below the 90% zone. It is apparent that any shelf life derived from the intersection of the lower 90% confidence bound and the 90% potency value has a 95% confidence level. In other words, there is only a 5% chance that our estimate of the shelf life will be too high. In fact, there is an additional safety margin built into most estimates of shelf life in that the period of time determined as described above (termed by A. J. Smith the *conformance period*) is usually significantly greater than the period defined as the shelf life. Suppose that for three separate pharmaceutical products we obtained 95% confidence estimates of the conformance periods of 13.2, 26.1, and 39.4 months. We would probably assign shelf lives of 12, 24, and 36 months to the three products. The difference between the conformance period and the assigned shelf life provides an extra stability reserve.

Those conversant with kinetic theory as outlined in Chapter 2 may wonder if the order of reaction affects the form of graph obtained as shown in Fig. 1. It might be felt that if the degradation process is governed by first-order kinetics, the plot would yield a curve rather than a straight line. In fact, since this type of plot only covers potency values from 100% down to 90%, both first and zero kinetic processes appear to be essentially linear. Yes, there are some degradation processes (3) that do produce nonlinear plots, but fortunately these are remarkably rare.

Shelf life values are normally assigned to a product rather than a batch. In order for such a practice to be legitimate, there must be reliable data that shows that, for at least three batches of the product, there is no significant difference in the slopes or the intercepts of the types of plot shown in Fig. 1. In those instances, where this level of batch similarity cannot be demonstrated, it might be possible to assign a shelf life based on a worst-case scenario (i.e., the shelf life is based on the worst-case batch). In this situation, we probably need more than three batches so that we can be comfortable that we have indeed identified the worst-case batch.