jurisdictions the maximum shelf life that a regulatory agency will approve for a drug product is five years. (This restriction is hardly an onerous one, since even for a product with a five-year shelf life it is probable that over 95% of the product will be sold and used within thirty months of manufacture, providing all involved in the distribution process obey the first law of warehousing: FIFO—first in, first out.)

Since the evaluation of the stability of a drug product is highly specialized and esoteric in nature, reliance on the patient's suck-it-and-see organoleptic evaluation is of distinctly limited value. Thus governments in many parts of the world—most importantly in Western Europe, North America, and Japan—have, because of concerns about drug product safety, efficacy, and quality, found it appropriate to require some form of stability testing for drug products. However, it must be recognized that even before governments became active in this area many reputable companies were already giving attention to drug product stability and developing their own in-house approaches. The increasing intervention by regulatory agencies such as the FDA (U.S. Federal Food and Drug Administration) and the HPB (Canadian Health Protection Branch) stimulated standard approaches to stability testing in those parts of the world subject to their control (1). More recently, the process of globalization and harmonization has stimulated the development of world-wide standards. (This topic is further considered in Chapter 18.) It is now well accepted that stability is an essential property of drug products; thus the assignment of a shelf life is a routine regulatory requirement.

2. POTENTIAL ADVERSE EFFECTS OF INSTABILITY IN PHARMACEUTICAL PRODUCTS

There is a variety of mechanisms by which drug products may degrade, and thus a quite wide range of adverse effects that can occur.

2.1. Loss of Active

Obviously, loss of drug is of major importance in the stability studies of many pharmaceutical products. Unfortunately, one sometimes gets the impression that some regard this as the only adverse effect of drug product stability, This is, of course, not true, and for some products loss of active is not the critical variable that determines shelf life. However, it is certainly true that for many products loss of potency is of major importance. In general, we regard any product that contains less than 90% of label claim of drug as being of unacceptable quality. Therefore, for many drug products, determination of the time that elapses before the drug content no longer exceeds 90% (when the product is stored in conformance to label instructions) is an essential element in determining shelf life (2).

The essence of the conventional way of determining shelf life from loss of active is as follows. The potency of product stored at the appropriate temperature (25°C for products to be labelled "Store at Controlled Room Temperature") is determined as a function of time and the best straight line of potency as a function of time determined by least squares regression analysis (Fig. 1). Of course, because of analytical and sampling error there will normally be some scatter of the experimentally determined data points around the mean regression line. Thus in order to have a high comfort level about the shelf life that we will assign to the product, we use conventional