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Letter

Interpretation of Drug Stability Testing

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KEY WORDS: drug stability; stability-indicating assay; initial-rate method.

Taylor and Shivji (1) misattributed my review article (2), "Stability-Indicating Assay Methods for Drugs and Their Dosage Forms," and they misinterpreted the definition of a "stability-indicating assay" as requiring direct determination of intact drug. In fact, I wrote, "One could . . . measure intact drug by a highly selective method, measure total drug content nonselectively and estimate the decomposition products, or selectively measure both drug and decomposition products." They champion the so-called "initial-rate method," which depends on determining the rate of formation of degradation products after a small amount of decomposition has occurred. References they cite, however, show that this method cannot be applied to products that show more than one decomposition product unless all of them have been characterized. For example, they noted that mitomycin C gives several different (unknown) products on hydrolysis in acid or base and then suggested that the difficulty in applying the initial-rate method could be circumvented by using strongly alkaline conditions, under which only one product is detected.

Much of the literature on pharmaceutical stability comprises reports on experiments using conditions of prolonged and intense exposure to thermal, oxidative, or light stress without relation to what occurs under normal conditions of processing and storage. Some of these papers are cited in Ref. 1. Further, it is not uncommon that some reactions in pharmaceutical systems will proceed only to the exhaustion of a reactant or during the application of high stress during processing and then cease. Reliance on the initial rate of formation of a product in these instances is likely to be misleading. Roksvaag *et al.* (3) showed that decomposition of morphine in injections ceased when the oxygen in the headspace had been consumed. A study of the autoxidation of procaterol in tablets (4) showed a significant lag time before oxidation products were detected. This situation, too, would militate against application of the initial-rate method.

There remain some cavils on language used in the paper (1) as well as its conclusions. Synthesis precursors and chemical process by-products and decomposition products are all "impurities." Researchers would be well advised to distinguish those impurities usually present in the drug substance from decomposition products, albeit they are sometimes identical. "Potency" was used to describe the physicochemical assay value (1). This is usually understood as a measurement of biological effect. Unless a biological assay is used, the term preferred is "strength." Determination of the reaction mechanism is not an essential concomitant of stability testing. If a drug substance is found to be labile during preformulation studies, the reaction type should be determined at that time to guide the formulation process.

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