# Editorials

## Avoiding Common Flaws in Stability and Compatibility Studies of Injectable Drugs

Over the last decade, it has been my privilege (and burden) to spend thousands of hours reading, studying, evaluating, summarizing, compiling, and writing critiques of countless articles on injectable drug stability and compatibility for the *Handbook on Injectable Drugs* and as a consulting editor for the *American Journal of Hospital Pharmacy*. This body of work stretches back at least three decades, and yet the topic remains of contemporary interest. In an age when the practice of pharmacy is undergoing revolutionary changes, no other aspect of the traditional pharmacy function of preparing dosage forms excites as much interest among practitioners as injectable drug preparation. The stability and compatibility of injectable drugs and admixtures remains an enduring topic of hospital pharmacists' research.

One finds this continuing interest manifesting itself as a constant stream of published (and unpublished) articles. Over the years, the quality of stability and compatibility work has ranged from the impeccable to the impossible; this is no less true today. It is unfortunate when dedicated individuals work hard on a project, making a sincere effort, only to have their papers go unpublished because of serious flaws in the design or conduct of the studies. It is perhaps more unfortunate when such work does find its way into print.

Zellmer[1] has presented general guidelines for writing research papers for pharmaceutical journals. Prospective authors should review this article, which appeared in the *Journal*'s Research Methods column, and other articles in that series that are pertinent to their work. Among the papers on injectable drug stability and compatibility submitted to the *Journal* over the last several years, there are certain specific flaws that continue to appear with some regularity. It is these recurrent flaws that I address here.

**Completely Describe the Materials, Test Conditions, and Methods.** The drugs and other materials used in the testing should be completely described including sources and quantities or concentrations. Similar products from different suppliers may have differing formulations that can affect results. Varying the concentrations tested may also alter results. A combination of drugs could be stable and compatible at low concentrations but not at higher concentrations.

All conditions of the test should be included and thoroughly described. Some variables that are frequently unmentioned include the actual temperature, presence or absence of light, and container materials. The actual temperature should be specified because of the rather wide ranges permitted in the *USP* definitions. For example, *USP* room temperature is 15 to 30 °C. This may be fine for storing drugs but is hardly suitable when doing a stability study. Significantly different rates of decomposition may occur at 30 °C compared with 15 °C. Some drugs may be light-sensitive. Others may sorb to some plastics.

In addition, the analytical methods used should be described in detail. If this has been done in another published article, a reference to that article is usually satisfactory. Further, the way in which simpler, more basic items such as pH, color, and clarity are determined should be described. For example, was clarity determined by visual observation or was a nephelometer used?

The materials, test conditions, and methods should be described sufficiently well to permit replication of the study. If this can be done, then these important points have been adequately described.

**Use a Stability-Indicating Assay.** The most common flaw is the failure to use an analytical method that has been demonstrated to be stability-indicating. It is incumbent on researchers to demonstrate that the method they are using will detect and separate the intact drug in the presence of its decomposition products and other drugs and components. Failure to do this will make the results suspect. How could such results be trusted if decomposition products or other drugs may be interfering with the test? Sadly, an otherwise acceptable study with original stability data can be transformed into a simple check for visual compatibility when the assay data are suspect.

A previously reported method that has been demonstrated to be stability-indicating for a drug and its decomposition products can sometimes be used *exactly* as published. Any important change in a variable of the method such as solvent composition will require demonstrating that the method remains stability-indicating.

Sources for such methods are not always easy to find. Analytical methods from pharmacology studies are designed to detect a drug and metabolites in body fluids. Such methods may or may not be directly applicable to stability and compatibility studies. All too often, *USP* procedures have been used because they are easy to locate and are "of-

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ficial." However, many *USP* assays are not stability-indicating.

More often than not, a modification of an existing method or an entirely new method will be required, which necessitates that the researcher prove that the assay is stability-indicating. Usually this is done in one of two ways. The fresh intact drug can be subjected to severe stress, such as extremes of pH and intensive heating, to intentionally decompose it. Alternatively, a solution of the intact drug can be spiked with known decomposition products. A stability-indicating method will accurately and selectively detect intact drug, separating it from decomposition products and other components of the solution. If decomposition products or other components interfere with the response of the drug, then the method cannot be regarded as suitably stability-indicating.

**Perform an Analytical Determination at the Outset.** A time-zero determination of drug concentration is essential. Without such a determination of initial concentration, there is no definitely known starting point. Often, it becomes impossible to make any definitive statements regarding changes in drug concentration and, therefore, drug stability. To simply assume that the initial concentration is the intended target concentration is not valid. Too many chances for error exist in making the test solutions. In addition to simple human error, variations in drug fill volume and concentration from the manufacturer, solution volume overfills, and syringe variability may contribute to an uncertain starting point. Without much difficulty, one can conceive of combined variations yielding a starting concentration of 80 to 120% of the target concentration. Erroneous conclusions can result from smaller variability than this.

Unless a time-zero analysis of the test solutions is performed, one is in the position of trying to determine the distance a traveler has come when his starting point is not precisely known, only his present location. An approximation, not a definitive result, is the best that can be achieved.

**Use Replicate Assays at Adequate and Appropriate Intervals.** Initially and at all test intervals, multiple assays of multiple test solutions should be performed. Too often only a single determination of a single test solution is reported. Performing several determinations on replicate test solutions at each interval will help to increase confidence in the accuracy of the results obtained by minimizing the effects of assay variability and human error. Erroneous outliers will be more easily detected. Although the number of samples tested at each interval should be tailored to the specific study requirements, as a general rule, duplicate assays of three replicate test solutions are considered a minimum.

In addition, the intervals at which the determinations are made should be appropriate for the adequate determination of the drug's stability and compatibility. If more than 10% decomposition resulted in a test solution in 24 hours, then the importance of intermediate assay intervals (e.g., 4 hours) to define stability limits becomes apparent.

**Make the Conclusions Fit the Results.** Flaws that fall into this category may be of several types. One prominent type is presenting overly definitive conclusions. Authors are generally encouraged to reach definite, firm conclusions from their data rather than hedging or qualifying their results. In most cases this is good. However, no author should state definitive conclusions that are not clearly established by the results. Such "conclusions" are in reality conjecture. Conclusions should be only as definite as all relevant facts permit. An example would be a study of drug stability and compatibility using an ultraviolet spectroscopy analytical technique that has not been demonstrated to be stability-indicating. A lack of changes in the UV spectra would not *definitively* show that the drug is stable. Rather, the conclusion should be simply that no changes in the UV spectra were observed. A conjecture, labeled as such, that this result supports the possibility that the drug is stable could be made. (Better yet, use a stability-indicating assay in the first place!)

Also, conclusions should take into account all of the data. Failure to consider inconvenient or puzzling results in order to simplify conclusions is inaccurate and misleading.

Another problem is the failure to apply adequate qualifiers to reflect uncertainties or the actual conditions of the study. One example would be a study of the compatibility of drug A and drug B in an infusion solution using an analytical technique that was only stability-indicating for drug A. The results cannot *definitively* show that the two drugs are compatible. The study could show that drug A was stable (or unstable) in the presence of drug B at given concentrations in the infusion solution. The conclusions should say that no statement regarding the stability of drug B can be made. (Ideally, *both* drugs should be assayed by stability-indicating techniques.)

One must also bear in mind that stability and compatibility are *relative* concepts. To be meaningful, they require qualifiers regarding time and conditions. Simple conclusions stating that two drugs are "compatible" or "incompatible" may not be particularly useful. Differing concentrations, temperatures, and time periods can affect the results. For example, more than 10% of a drug may decompose in solution in 24 hours at 25 °C. This would fit the conventional definition of an incompatibility. Yet the drug may be usable for some lesser time period such as 8 or 12 hours. Applying the concept of utility time or time to 10% decomposition ($t_{90}$) may be more useful than saying the combination is incompatible. Again this shows the importance of having sufficient data points to adequately define a drug's stability.

**Conclusion.** These common flaws have been the source of frequent aggravation and frustration to authors as articles have to be reworked, rewritten, or even abandoned. If these problems are avoided at the outset in the design of the study and through project completion and writing of the paper, much wasted effort will be eliminated and higher quality papers on drug stability and compatibility will result.

1. Zellmer WA. How to write a research report for publication. *Am J Hosp Pharm.* 1981; 38:545–50.

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