Sampling Errors in Validation

Patricia L. Smith

EDITOR’S NOTE

Dr. Smith is also the author of A Primer for Sampling Solids, Liquids, and Gases Based on the Theory of Pierre Gy (1).

ABSTRACT
Recognition of sampling errors and their impact on data variation is an important consideration in pharmaceutical and medical device validation. The evaluation of suspect data may be enhanced by consideration of sampling errors. Validation and compliance professionals must always be aware of the potential for sampling errors and their impact. Sampling errors may greatly influence validation data, cause incorrect judgments, influence trending, add variation, and otherwise significantly affect data accuracy and precision.

Sampling errors may be generally categorized as Material Errors, Process Errors, Sample Errors, and Laboratory Errors. Ten specific individual sampling errors have been identified. Material errors include Fundamental Error, Grouping and Segregation Error, and Nugget Effect. Material variation is due to its composition, its distribution, and inherent material non-uniformity. Material variation is often not fully appreciated and may impact all other sources of variation. Process errors include Non-periodic Process Errors and Periodic Process Errors. Process variation is fairly well understood and contributes to data variation in generally predictable ways. Sample errors include Sample Definition, Sample Collection, and Sample Handling. Sample selection (i.e., sample definition and collection) is often not defined to a sufficient extent to prevent errors and excessive data variation. Laboratory errors include Analytical Error and Data Error. Laboratory error contributions to sampling errors are frequently overlooked. Data errors may occur in processing, sampling, and in the laboratory.

Example actual occurrences of sampling errors directly impacting validation are described.

INTRODUCTION
Sampling is often an overlooked component of any validation activity. Validation protocols may simply identify required samples to test a process without adequately describing the correct method for actually obtaining samples and preserving their integrity. Manufacturing personnel remove the specified samples and place them into apparently suitable containers. Samples are transferred to the lab (sometimes a contract facility at another site) for testing without specific instructions. Data are generated and results calculated per general procedures. When results are not acceptable or are not as expected, an investigation is conducted addressing the usual sources of problems—usually

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not including sampling. Validation personnel must recognize that sampling is a vital component of the validation effort. Sampling errors may be the sole cause of failing data or significantly contribute to unexpected or highly variable results. Sampling errors may be overtly obvious (e.g., degradation of a frozen sample by exposure to excessive heat). Sampling errors may also be completely invisible (e.g., data transformation by means of improper calculation software). In any case, sampling is an important consideration in pharmaceutical and medical device validation and must be considered as such by validation professionals.

This discussion addresses types of sampling errors relevant to validation that have been identified in previous publications. Ten distinct sampling errors have been identified. Example actual situations in which various sampling errors caused validation problems are presented.

SAMPLING ERRORS
Sampling errors were originally reported by Gy (2) in 1992. Pitard (3) and Smith and LeBlond (4) have identified additional sampling errors. Gy introduced and explained seven errors including fundamental error, grouping and segregation error, delimitation error, extraction error, preparation error, long-range non-periodic process error, and long-range periodic process error. Pitard identified two additional sampling errors. These include the nugget effect and analytical error. Smith and LeBlond described the data error.

Sample Error Grouping and Individual Sampling Errors
The 10 sampling errors have been categorized into four major groups. Terminology describing these 10 errors has also been adjusted for better understanding and to reflect common usage. The four groups of sampling errors and their respective specific errors are as follows:

- **Material errors.** These include the fundamental error, which is generated by the composition heterogeneity; the grouping and segregation error, which is generated by distribution heterogeneity; and the nugget effect. Material errors may impact process errors, sampling errors, and laboratory errors.

- **Process errors.** These include non-periodic variation and periodic variation associated with the process.

- **Sampling errors.** These include sample definition, sample collection, and sample handling errors.

- **Laboratory errors.** These include analytical errors and data errors. Essentially all above errors may affect laboratory errors, and conversely, may be affected by laboratory errors.

The error groups and individual errors are depicted in the Table. The Table identifies the four respective sample groups and enumerates each specific error. Errors that are affected by other individual errors are also indicated. For example, material segregation (generating error #2) may occur during processing (errors #4 and 5), during sample handling (error #8), and during sampling in the laboratory (error #9). Alternately, test data (error #10) generated in the laboratory may have been affected by material errors (error #2), sample errors (errors #6, 7, 8), analytical errors (error #9), and other data errors (error #10). Brief discussions on the above groups and individual errors follow.

MATERIAL ERRORS–FUNDAMENTAL ERROR, GROUPING AND SEGREGATION ERROR, AND NUGGET EFFECT
Material errors comprise three distinct errors. These include fundamental error, grouping and segregation error, and nugget effect. Material variation is composed of the variation due to its composition, its distribution during handling of the sample, and inherent non-uniformity (nugget effect) in the sample.

Material variation is often not fully appreciated. An aspect of data variation that is quite important is the variation in the material itself. It underlies all the other contributors to data variation. The nature of the material, how it “behaves” in various situations such as in blenders, and how it is “presented” to us for sampling must be well understood to minimize sampling variation. Material errors are inherent in all phases of sampling and may exacerbate process errors, sampling errors, and laboratory errors.

Error #1. Fundamental Error
The fundamental error relates to the nature or composition of the material. This error is inherent when the material is sampled and is unavoidable. The material we sample varies in its composition or constitution, which generates the fundamental error. For example, a mixture of powders used to manufacture a pharmaceutical tablet contains the active drug, binders, fillers, and other formulation components. These components have different particle sizes, particle densities, particle shapes, surface charges, and other differences. This type of material variation is called the composition variation.
heterogeneity. Because the particles are not perfectly identical and thus the material not perfectly uniform, our samples will not be a microcosm of the lot. Even with “perfect” sampling, there is no such thing as a “representative” or “accurate” sample. Samples are a subset of the lot, and they are representative and accurate only to within the degree of precision we are willing to tolerate. Consequently, just the act of sampling generates an error, and so the sample is not perfectly representative of the lot. This is the fundamental error. The size of the error depends on the physical properties of the particles and also on the amount of material taken in the sample. By reducing the maximum particle size or by increasing the weight or volume of the sample, we can decrease the fundamental error. But we can never eliminate it. Validation professionals must be aware of the composition and properties of the material being sampled and be alert to the potential for the fundamental error.

**Error #2. Grouping and Segregation Error**
The grouping and segregation error addresses how various particles are distributed both in the lot and at the particular place where we take a sample. Differences between individual particles determine how they are distributed in the lot as well as “locally.” They may segregate during transport or when transferred from one container to another, for instance. This variation in particle location is the distribution heterogeneity. Variation in our data arises not only because of the composition heterogeneity but also because we sample bulk material as “clusters” of particles. We do not sample particles individually. Further, the material is never perfectly blended: it always has some degree of settling or segregation. Even if a near perfect blend was achieved, we lose that uniformity when we transfer the product from blender to drum to hopper. Consequently, we incur the distribution heterogeneity, which generates the grouping and segregation error. Taking smaller increments to make up the sample can reduce this error. It can also be reduced by mixing. This also has applications in the lab, where it is beneficial to blend a sample (not combine separate samples) before taking an aliquot for testing. Unfortunately, perfect blending is impossible, so we can never fully eliminate this error. By awareness of the composition and properties of the material being sampled, validation professionals should know the potential for grouping and segregation errors.

**Error #3. Nugget Effect**
The nugget effect is a sampling error caused by non-uniformity in material composition and is one cause of data values that we might consider outliers. This error is exemplified in the mining industry when prospecting for gold. An area of land may be sampled to determine the presence of gold. The area to be sampled may have a low level of relatively uniform gold concentration, but may also have localized high concentrations of gold. If not properly sampled, it is these high concentrations that may cause our test results to be erroneous. Results may be skewed high or skewed low depending on the sample we withdraw. If we preferentially sample the high concentration “nugget” area, we overestimate the true concentration in the total land area of interest. If we do not measure the high concentration area, we underestimate the true concentration in the total land area.

The nugget effect may occur in sampling pharmaceutical or nutritional materials such as natural products.

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**Table: Sampling errors.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Error #</th>
<th>Error</th>
<th>Affected By</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Fundamental</td>
<td>NA</td>
</tr>
<tr>
<td>Material</td>
<td>2</td>
<td>Grouping and segregation</td>
<td>NA</td>
</tr>
<tr>
<td>Material</td>
<td>3</td>
<td>Nugget effect</td>
<td>NA</td>
</tr>
<tr>
<td>Process</td>
<td>4</td>
<td>Non-periodic</td>
<td>Material errors, data errors</td>
</tr>
<tr>
<td>Process</td>
<td>5</td>
<td>Periodic</td>
<td>Material errors, data errors</td>
</tr>
<tr>
<td>Sample</td>
<td>6</td>
<td>Sample definition</td>
<td>Material errors, data errors</td>
</tr>
<tr>
<td>Sample</td>
<td>7</td>
<td>Sample collection</td>
<td>Material errors, data errors</td>
</tr>
<tr>
<td>Sample</td>
<td>8</td>
<td>Sample handling</td>
<td>Material errors, data errors</td>
</tr>
<tr>
<td>Laboratory</td>
<td>9</td>
<td>Analytical</td>
<td>Material errors, sample errors, data errors</td>
</tr>
<tr>
<td>Laboratory</td>
<td>10</td>
<td>Data</td>
<td>Material errors, sample errors, laboratory errors, data errors</td>
</tr>
</tbody>
</table>

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Nuggets may be individual particles, clumped materials due to moisture or electrostatic charge, or other localized regions of high ingredient concentration in the material to be sampled. If the “nuggets” were the active ingredient and were a highly potent material, the presence or absence of a nugget in a tablet or capsule could have significant impact on the patient.

A few abnormal particles in a sample can have a devastating effect on estimation. For example, we may have material containing a relatively low concentration of desirable content but with highly variable composition between particles. Those particles with the higher, atypical content would be considered nuggets. In another instance, raw material that gained some moisture may clump together. If it were preferentially selected, it would appear quite unusual when the lot itself may be acceptable in terms of the overall characteristics. These uncommon samples can mislead us. Again, validation professionals must be knowledgeable of the composition and properties of materials being sampled.

**PROCESS ERRORS—NON-PERIODIC AND PERIODIC PROCESS ERRORS**

Process errors include non-periodic process errors and periodic process errors. Process variation is fairly well understood and contributes to data variation in generally predictable ways.

**Error #4. Non-Periodic Process Errors and Error #5. Periodic Process Errors**

There are two sources of process variation: non-periodic errors and periodic errors. Non-periodic process variation is non-random and results from process changes showing data shifts and trends. We might know there was a process upset or that material from a new supplier was non-uniformly introduced into the process—both are examples of non-periodic process variation. Periodic process variation is also non-random and results from cyclic behavior. Temperature and humidity as related to storage conditions in the summer (in an inadequately environmentally-controlled warehouse) are examples of cyclic behavior. An optimal sampling strategy, including such things as sampling frequency and stratification plans, is beyond the scope of this article. Gy describes graphical and analytical techniques for examining both non-periodic and periodic process behavior (2).

Processes change over time, and these changes occur for many different reasons. Tracking measurements on assorted different characteristics is our way of making sure the product has the quality we need. We also use tracking to determine if something unexpected has happened along the way. We obtain these measurements by sampling the material at different points in the process.

Process measurements will always show some variation. We expect this. However, a measurement that is “too different” from others in the past is an indication that something has changed in the process or that the sample was somehow unrepresentative. If we cannot find a source for the unusual measurement in the process, then we turn to other possible causes. Two places to look are the material itself and how it is “presented” to us for sampling. If the material has properties that are highly prone to sampling problems such as segregation after transfer, process variation errors are exaggerated. Further, incorrect sample handling and sample selection can bias process results.

**SAMPLE ERRORS—DEFINITION, COLLECTION, AND HANDLING**

Sample errors include sample definition, sample collection, and sample handling. Sample selection is rarely correct and is not proscribed to a sufficient extent to prevent errors and variation.

In the following discussion, we combine sample definition and sample collection as “sample selection.”

**Sample Selection—Sample Definition and Collection (Error #6. Sample Definition and Error #7. Sample Collection)**

The most misunderstood cause of data variation is incorrect sample selection, which includes sample definition and sample collection. Sample definition is determining what subset of the lot material will be in the sample. Sample collection is physically obtaining the material identified to be in the sample. The principle of correct sampling must be followed to reduce errors in sample selection. Every equal-sized portion of the lot must have the same chance of being in the sample. The sample integrity must be preserved both during and after sampling.

This principle is the “bulk sampling” version of simple random sampling that is used in statistical sampling. Recall that randomness is not the same as haphazard. Randomness is a well-defined process that can be repeated. The results of the process may be different, but the process itself is the same. Think about drawing numbers for the lottery. The process is the same, but the results vary substantially.

In simple random sampling, units in the population are chosen individually (one at a time), with equal probability (every unit has the same chance), and completely
at random (using a well-defined random process). Not one of these three aspects can be accomplished with bulk sampling! The most obvious departure is that we do not sample individual units or items. Bulk material consists of many, many particles. We cannot choose them individually. We select particles in groups, always of different sizes, even if only slightly, by weight or volume. Thus, we are not sampling with equal probability. Finally, we almost never sample completely at random.

It is quite clear that the idea of individual selection cannot be met in bulk sampling. By way of example, let’s look at the other two aspects causing difficulty: equal probability and randomness. They are very much related. If a sample port limits our access to just surface material, then we are not sampling randomly, and material far from the port has no chance of being in the sample. If we have material moving along an open conveyor belt, then a “grab” sample taken from the side does not follow the principle of correct sampling. Material on the opposite side has no chance of being in the sample, so the selection process is neither random nor correct. Further, if the properties of the material to be sampled are highly prone to sampling problems such as having significant differences in particle size, then problems in bulk sampling are more likely to occur.

Material that is not well mixed, for example, is especially susceptible to violations of the principle of correct sampling. An incomplete blending operation can result in highly segregated material; hence sampling from the top or side will result in a biased sample. Particles of different sizes have a tendency to separate during transport or transfer. In these cases, we see that the grouping and segregation error previously discussed compounds the variation and bias from incorrect sampling.

Error #8. Sample Handling
Sample handling is generally considered part of the broad category of sampling. It addresses the preservation and integrity of the sample, both during and after sampling. Sample handling speaks to physical or chemical changes that alter the sample’s material composition and the characteristic of interest, which in turn change our measurement. Sample handling is often overlooked as a cause of sampling problems. For example, a sample may be correctly taken on the production floor, packaged, and sent to the laboratory for analysis. When the lab receives the sample, however, the sample has significantly changed. The particle size distribution may be altered due to abrasion, or other changes may take place because the proper storage temperature of the sample has not been maintained during transit.

Sample handling is specialized and generally described to fit particular situations. Typically, our procedures for this are very specific and depend on the material we are sampling. For instance, we know that some material needs to be covered or kept refrigerated until analyzed. Other material may require a special pressurized container. We recognize that samples not handled properly can contribute to increased data variation and even wrong values.

When unusual data cannot be explained by something atypical in the process or lab, then sampling is usually blamed. Unfortunately, the aspect of sampling we are most familiar with is sample handling—so this is where we focus. While it is an important aspect of sampling, there is much more that is ignored. In most cases, it is because we are unaware of the other aspects of sampling such as sample definition and collection that may cause variation.

Sample handling must not be taken for granted. Validation protocols and sampling instructions must clearly specify sample handling requirements for production operators as well as for laboratory analysts.

LABORATORY ERRORS—ANALYTICAL AND DATA ERRORS
Laboratory errors include analytical error and data error. Laboratory errors are well-recognized and well-documented. Laboratory errors affect process data. Data errors may further exacerbate process errors, sample errors, and laboratory errors.

The lab category includes errors from all sample preparation activities and analytical testing. Sample preparation errors include sample definition, sample collection, and sample handling. These considerations when taking the sample similarly apply in the lab when the laboratory analysts prepare the actual material to be tested. For example, a 100-gram sample of powder mixture is submitted for testing in the lab. The laboratory analyst only needs 5 grams for sample preparation and testing. The definition, collection, and handling of the 5-gram sample introduce variation into the final test data. After the 5-gram sample is prepared using procedures such as grinding, extraction, dilution, and so on, the sample is ready for instrumental analysis. If the material properties are highly prone to sampling problems such as material segregation due to different particle size, the sample preparation errors may be significant. Actual testing with an analytical instrument also contributes an analytical error.
Error #9. Analytical Error

The category of lab error includes sample preparation in the lab, which usually consists of several steps. Analytical error also involves the error due to the analytical instrument. This error may be determined by performing an instrument precision study in which the same sample is re-injected through high-performance liquid chromatography (HPLC) multiple times and mean and standard deviation are calculated. The analytical error may also include human performance variation in the laboratory procedure including such things as incomplete dissolution, splattering during heating, and reading the liquid meniscus improperly. Use of multiple standards will also contribute to data error. Analytical instruments include pumps, timers, transfer mechanisms, and other mechanical equipment, all of which contribute variation to the final test result.

We monitor lab results by using control charts. We use them on standards. We might also use them on process data. Unusual values or patterns can be flagged and examined. In such situations, our typical first steps might be to check that the instrument was calibrated, rerun a standard, or retest the sample. Unusual process values are typically attributed to process variation, and the lab might contact the appropriate process personnel to see if they have an explanation. If not, and if the lab can find nothing wrong with its analysis, then “sampling” is often blamed. But as we have seen, two of the components of sampling, sample definition and collection, are not often investigated very thoroughly, either inside or outside the lab.

Error #10. Data Error

Data errors are included in the laboratory error category because that is where they are more likely to occur. They can, however, arise anywhere in the process or in sampling. They consist of all mistakes and inaccuracies that occur in manual data recording, data transfer, and data treatment, whether done manually or by computer. Data errors that have been identified include the following:

• Data recording. This refers to mistakes caused by sampling personnel or laboratory personnel in recording sample weights, analytical results, and other manual recording of data. Accurate and correct data recording is fundamental to the sampling process. This refers to inadvertent mistakes by personnel in recording sample weights, transposing numbers, forgetting numbers, and so on as might happen in the manual recording of data.

• Data transfer—rounding, manual, and electronic errors. This refers to errors or mistakes in the transfer of original data. Transfer may occur by human intervention or by electronic means. Accurate and correct data recording is fundamental to the sampling process. Data integrity may be damaged inadvertently by personnel who are simply transferring data or original records, compiling lists, entering data into computer systems, and so on. Data may also be transferred electronically between different computer software programs.

• Calculations. Manual calculations performed by humans are prone to mistakes. Even when all input numbers are correct, mistakes can occur. Calculators may be operated incorrectly, equations may be misread, and so on. People unfamiliar with algebraic notations may be asked to perform calculations because they are presumably so easy. Electronic calculations should be much less likely to produce errors. However, when impacted by humans, these methods may produce errors.

• Data treatment software. This refers to an incorrect choice of data treatment program or options within a software program. Data error may be caused by an incorrect choice of data treatment program. Often decisions are not based on raw data themselves, but on statistics that are calculated from the raw data. Even if the integrity of the raw data is properly preserved during recording and transfer, an inadequate computing system or use of an inappropriate statistical procedure during analysis may lead to an incorrectly calculated or inappropriate decision statistic. For example, complex calculations such as regression may be performed using computer software that does not preserve an adequate number of digits in its computations. An example of an inappropriate decision statistic in MS Excel occurs when an analyst erroneously selects STDEVP() to calculate the standard deviation of a small sample rather than the appropriate function STDEV().

SOME EXAMPLE SAMPLING ERRORS IN VALIDATION

The above categorization of sampling errors indicates that they may occur at any time during the validation process. The following examples demonstrate.

Manufacturing Floor Sample “Perfection”

Process validation was being conducted on a blending process in manufacture of a tablet dosage form. The validation protocol required that the manufacturing operator withdraw 12 samples from the mixer using
a thief. Each sample was required to be between 0.2 and 0.3 grams. When all samples were tested by the laboratory to determine the active drug content in the blend, test results failed and test data showed unexpectedly high variability. Further examination of the sampling data showed that all samples submitted by the operator were between 0.248 and 0.252 grams, a highly unlikely occurrence. Further discussion with the operator indicated that he made sure that all samples were in the middle of the target range by removing excess powder by pouring powder from the sample container, removing powder with a spatula, adding powder back into the sample, and so on—whatever was needed to submit a perfect sample (in his mind) to the lab. These manipulations caused powder segregation, loss of active ingredient, and ultimately significant data variation. A subsequent trial in which sample weights were not manipulated resulted in successful validation data.

**Data Recording**
The manufacturing operator removed samples from the drying oven after completion of a drying process. Sampling was recorded on a validation sampling page that included a sample number, sample weight, and oven shelf number. His sample recording page had a number of cross-outs and entry mistakes. The operator expected to be criticized for his sloppy sampling page, so he rewrote the page. In rewriting the page, several sample weights were incorrectly rewritten so that weights did not correspond with the sampling location. The laboratory results indicated several high values that should have been able to be correlated to high weights. However, because the sampling records had been incorrectly rewritten, correlation was initially not possible. Further discussion with the operator and retrieval of the original sample page enabled the correct correlation to be made.

**Laboratory Efficiency**
A laboratory routinely optimized sample test performance through use of formatted data sheets for HPLC analyses. This sheet required all samples to be tested in a specified order related to the concentration of the unknown. Samples from a process validation performance qualification were submitted for analysis. Laboratory personnel followed their internal procedures regarding use of data sheets. However, this procedure destroyed the continuity of the process validation samples as sampled during the process. Because new laboratory analytical standards were freshly prepared each day, distinct differences in data were observed depending on the assay day and associated standard. Better communication between validation personnel submitting sample and laboratory personnel explaining the importance of maintaining sample continuity would have prevented this problem.

**Massive Data Transfer**
Process validation of a tablet compressing process was conducted. Testing was conducted according to US Food and Drug Administration guidelines (5) in which 140 individual tablet samples were required to be tested for each lot in the validation protocol. A total of 7 lots were tested to validate the manufacturing process for a multiple dosage strength product. Nearly 1000 test results were thus supplied to technical personnel from the lab. These test results were then transferred to Excel spreadsheets for calculations and graphing. Test results were simultaneously transferred to Microsoft Word documents for preparation of validation reports. When reports, calculations, and original laboratory data were reviewed for consistency, many errors and inconsistencies were found. These errors were technically insignificant, but were very embarrassing to the organization when observed by FDA auditors. Errors were a result of the great number of data transfers, insufficient time to verify transfers, tight timelines, and inadequately trained personnel performing data transfers and verification.

**Improper Use of Sampling Thief by Untrained Personnel**
This incident describes validation of a mixing process. Sampling of the powder blend from a large-scale mixer was to be accomplished by means of a five-chambered sampling thief. A total for 30 powder-blend samples (six insertions yielding five samples each) were required from prescribed sampling locations. Sampling was accomplished from a second-floor catwalk. Samples were taken and delivered to the laboratory for analysis. Test results of thief samples indicated excessive variation in drug concentration that failed validation requirements. Review of documentation of sample weights from the sampling protocol was acceptable. All laboratory records were acceptable. There was no apparent reason for the failing results other than actual failure of the mixing process.

A second trial was conducted using identical materials, procedures, and personnel. However, the second trial was observed by multiple technical personnel and management. When the manufacturing operator
sampled the mixer, he did not completely insert the sampling thief into the mixer—only two (of five) sample cavities were filled. He then repeated the insertions as often as necessary to obtain the 30 total samples. The operator did not follow the sampling directions as specified in the protocol. When questioned about his sampling method and technique on the two validation samplings, the operator admitted that he had never previously used the sampling thief, and that he was afraid of heights. He was very nervous about the sampling from the second floor catwalk. He was unaware of proper operation of the multi-chambered thief and had never been trained.

Another full-scale trial was conducted. A trained operator performed sampling as specified in the validation protocol. All results were acceptable.

**Laboratory Testing on “Same Day”**

Sampling of a tablet product for dissolution testing was accomplished as directed in the validation protocol. Tablets were sampled and placed in sample bottles for transport to the lab. After receipt, laboratory personnel immediately conducted dissolution testing as specified. Per protocol, testing must be conducted on the same day as samples were received. The dissolution part of the test procedure was completed as specified. However, HPLC analysis was not done due to equipment problems. Repair and new setup were not accomplished until the next morning. The lab supervisor interpreted the “same day” requirement specified in testing instructions as “24 hours.” Because the HPLC analysis was initiated within 24 hours, results were reported to the validation group without further communication. Analytical results did not pass acceptance criteria. Investigation of possible causes for the failure was then initiated. Material problems, formulation problems, process problems, and other potential causes were investigated. No one was told about the equipment failure, how the samples were stored, or other considerations that might be relevant. It was only after several days of investigation that the laboratory supervisor inadvertently commented about HPLC problems and the delay in analysis. If the solution was not immediately assayed, it should have been frozen. Room temperature storage of solutions caused drug degradation resulting in the validation failure.

**SUMMARY**

This discussion has described sampling errors relevant to validation in pharmaceutical and medical devices. Recognition of sampling errors and their impact on data variation is an important consideration in validation data evaluation. Four general categories comprising 10 individual sampling errors have been identified. Material errors caused by inherent material properties are relevant to essentially all other errors. Other categories of sampling errors include sample errors, process errors, and laboratory errors. Sampling errors may occur at all times during validation—during processing, during testing, and during analysis of data.

Sampling errors may greatly influence validation data, cause incorrect judgments, influence trending, add variation, and otherwise significantly affect data accuracy and precision. Validation and compliance professionals must always be aware of the potential for sampling errors and their impact on validation data and analysis. Sampling must not be overlooked as a critical aspect of successful validation.

**REFERENCES**