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UNDERSTANDING AND REDUCING ANALYTICAL ERROR IN LABORATORIES

ABSTRACT
In recent years over half of Wysowl's clients have identified weaknesses in their analytical processes. Clients as varied as metallurgical and petrochemical plants, pharmaceutical operations, manufacturers of thermal ceramics, optical lens producers and wool processing plants all depend on sound analytical techniques and results. In several cases, techniques have been substantially improved and analytical error has been halved.

DOES A PROBLEM EXIST?
Perhaps the issue of greatest concern is that several companies were unaware that a problem existed. For instance, one firm was convinced that the analytical error for a particular measurement was about ± 1.5%. They regularly ran control samples, and were confident of their capability. It is important to state here that the only way we know to obtain utterly reliable measures of analytical error is to run some blind controls. There is no doubt that technicians treat control samples differently to production samples. Often this differentiation is subconscious. Nevertheless, it is present. When data from blind controls were examined, they displayed a variability of ± nearly 3%. The analytical error was twice what the lab manager thought it was. Given that the specifications were ± 5%, a significant problem existed, with many batches failing final test.

As it transpires, the figure of ± 1.5% was the analytical error of the analytical instrument alone. It did not take into account technician to technician variation, temperature and humidity changes or error caused by different batches of reagent. The blind controls included these sources of variation, and therefore a larger analytical error was recorded. It is worth noting that even the blind controls could not include any sampling error that might be present. In most cases examined recently, the larger proportion of the additional variation detected by blind controls has been traced to technician-to-technician variation, unidentified instrument malfunction and variation in sample preparation. Other areas worth checking include instrument-to-instrument variation and variation in chemicals such as reagents and catalysts.

Another common point of concern is that very few blind controls conducted by clients in recent years have exhibited good statistical control.
Some labs have claimed that even though their results could be better, that they meet current requirements. Several issues rise here. Firstly, how confident can anyone be of

results from an analytical process that is known to lack stability? One of the first lessons Shewhart taught us was that a process had no known capability until it was stable. Secondly, the history of analysis is that with time, ever greater precision is called for. In labs, precision **must** be continually improved, because greater precision will always be called for. It seems wise to be preparing for the future by continually improving analytical techniques so that we gradually approach the higher standards the future is sure to demand. The alternative is to wait until the future's demands hit us whilst we are ill-prepared. Finally, surely the customers of any analytical process deserve the best service that can be provided using current technology.

A PERSONAL ANECDOTE

As a brand new Second Lieutenant in the Corps of Engineers, I was given some training in civil engineering with a strong bias towards design and construction of roads and airfields. A necessary component of this training was testing of materials. Our training included not only work in our own lab, but also several field visits to labs in the construction industry. Although over twenty years have passed since these experiences, a few aspects remain as clear as if they occurred yesterday. One is the laboratory managers themselves. They were so alike that I began to suspect that somewhere there existed a mould in which these men were manufactured. Most appeared to have had all the milk of human sweetness sucked out of them, if it were ever present. They were dry, taciturn technical types who cared little for anything except their work. Most had all the people skills of a house brick…….but they were technically excellent, as were their labs.

It simply never occurred to we construction types to question the lab results, because we knew how thorough and precise they were. Lab managers networked to provide blind controls and to conduct audits for each other. Precision was the focal point of their existence. They were nothing short of excellent. Sometime during the past twenty years, many laboratories have lost this reputation for cooperation, technical excellence and precision. Another aspect that bears mention was that in the road construction industry the labs themselves collected the samples. They had control over the entire analytical process, which includes sampling.

WARNING SIGNS

Usually, as lab performance starts to slip away, some warning signals are available. Too often, they are missed. One such signal is a lack of faith in analytical results by the production folk. If production people note that a check sample often produces a result markedly different from the original production sample, their faith in the analytical system will be undermined quickly, even though the problem may be infrequent and despite the fact that sometimes these differences are a result of poor sampling by the production people themselves.

Another warning signal occurs when batches fail final test. If the subsequent study generally finds that most of these batches do in fact meet specifications, we are forced to question why the batches failed in the first instance. The data from one pharmaceutical factory showed that over 60% of all batch failures were, in fact, due to analytical error. Most batches eventually found their way to market, but not before a considerable delay with the accompanying distribution problems as well as additional costs.

FAITH IN THE SYSTEM

There are too many cases where the production people have lost more than a little faith in the capability of the analytical processes that serve them. Often, this results in many check samples being processed. This not only increases costs, but also it can create bottlenecks in an otherwise orderly flow of samples and test results and cause delays in processing samples. If we measure the performance of an analytical process in terms of cost and service, things could be better in many companies.

SAMPLING ERROR

As previously mentioned, not even blind controls can detect sampling error. One

anecdote will illustrate the dangers inherit in inadequate sampling. A pharmaceutical client produces an interim product in broth form. This broth can be highly variable. The procedure adopted to sample this material was to take a triplicate sample and then to average the three results. The procedure required the operator to open the vessel containing the liquid and to take a sample using a ladle. The sample was then transferred to a sampling bottle. This procedure was repeated twice more, with the liquid being agitated thoroughly during sampling.

For a variety of reasons, not the least being concern about variable results, the actual procedure used gradually drifted away from the approved method over time. The operators would take a sample with the ladle, and fill all three sampling bottles from the one ladle of material. Not surprisingly, the test results showed very good uniformity amongst these sets of three samples. They must do so. They are essentially the same material, decanted into three separate bottles.

When this case study was used at a subsequent seminar, one operator was visibly distraught on hearing the story. She was a relatively new operator, and was responsible for the sampling of this liquid on her shift. However, this was not the major cause for her distress. The major cause was that most of her work mates were laughing at what was, to them, a ridiculous procedure. However, that was how she had been trained to take the sample by senior operators.

One question Dr. Deming repeatedly asked during his seminars was, “What temperature does a thermometer measure?” He would play with the audience for a while before providing the answer, “Its own”. He was trying to teach us an important lesson that is closely related to sampling error. Remember that the lab does not test the process or the product, it tests the sample. If you take a different sample, new results can be anticipated. The precision of the entire analytical process can never be better than the precision of the sampling component. If there is much sampling error, a precise analytical instrument may be next to useless.

One way of expressing total variation is that the total variation = product variability + analytical variability + sampling variability. Too often we forget the last component and assume that the sample is representative of the entire process or batch. It is not. It never can be. All we can hope for is to get as close as feasible, and to know what the sampling variation is likely to be. Effective separation of sampling, analytical and process error can be achieved by a hierarchical study. The frequency with which sampling error is the most variable of these three components often surprises people.

No further detail on sampling will be offered here, except to suggest that it seems wise to occasionally audit sampling procedures. Clearly, sampling error can have a significant impact on analytical results, and needs to be considered.

UNDERSTANDING THE PROBLEM - BLIND CONTROLS

As previously mentioned, the only way we know to properly evaluate the degree of analytical error is to use blind controls. Numerous studies have shown that lab technicians do not treat control samples in the same way as they treat production samples. This is not a criticism. It is recognition that at a subconscious level, our motives and actions are not always what we think they are. None of us is proof to such behaviour.

In the example mentioned earlier where a ± 1.5% error was thought to exist, a drum of product was captured before being decanted into retail sized bottles. The liquid was agitated with an air hose to ensure uniformity (it is critical that the material being used for blind controls is as uniform as imaginable) and decanted into bottles which were refrigerated to ensure the material did not degrade. These bottles were steadily slipped into the stream of production samples and a record kept of their sample numbers so they could be separated from the true production

samples when the results were produced by the lab.

Note how it would be impossible for the lab technician to know whether the sample currently being tested was a blind control. These samples must present as normal production samples in the lab, meaning that production folk must be involved. In this particular case, the lab had initially declined a request to run some blind controls. The trial was eventually authorised by the factory manager and performed by a production manager. The lab manager did not learn of the trial until the results were shown to him by the factory manager.

Some lab people are afraid that data from blind controls will be used as a weapon against them. The evidence suggests the opposite. Experience shows that if such procedures are initiated by the lab in an attempt to improve and then guarantee a certain level of precision and service, that enthusiastic cooperation is the likely response from production people who see that they are the beneficiaries. In addition, because production people are a part of the process, they are more likely to have faith in the results from blind controls. Once such a partnership has been established an increased confidence in analytical data usually results in production folk calling for fewer check tests.

STUDYING THE DATA

Initially, two methods of analysis are recommended. If the blind controls are slipped into the production samples over time (as is usually the case), a control chart and perhaps a frequency distribution are the best places to start. Remember that when using a single point and moving range control chart it is essential to remove any special causes from the ranges chart to avoid corruption of the control limits.

Most labs already capture their data in such a way as to make stratification of the data for subsequent analysis simple. It is normal for test results to be logged in such a way that it is a simple matter to discover which technician and which instrument was used to produce a particular result. Also, these results normally have other relevant data logged with them. For example, date and time of day of the test.

Because of these records, stratification of the data by: technician; instrument; time of the day and batch numbers of reagent (for example) is generally quick and painless, which makes one wonder why it is so seldom done. One such stratification into time series showed that analytical variation in a pharmaceutical laboratory increased during hot weather. The air conditioning plant was unable to control temperature and humidity sufficiently and this variation was impacting on test results. Many of the batches that failed were a consequence of test data produced in the middle of a hot day.

Once the significant problems such as technician-to-technician and instrument-to-instrument variation have been conquered, a control chart of a series of blind controls is usually sensitive enough to detect even tiny changes such as might be caused by a change in the batch of reagent or catalyst being used.

PLANT TRIALS

It is common to discover that lab people have not been informed that a plant trial is being conducted. If the tests being conducted during the trial are inherently difficult, or for other reasons they tend to suffer from technician-to-technician and/or instrument-to-instrument variation, it is nearly always possible for the lab to limit the number of technicians and instruments used during the trial. This reduces the amount of background “noise” during the trial, making it easier to see the results of any changes made. If such precautions are not made, analytical error can screen small but important changes in the process during a trial.

HOW GOOD IS EXCELLENT?

Not all companies are experiencing problems with their analytical processes. For example, one smelter in the aluminium smelting industry has been excellent for years. The lab manager has been conducting blind controls since he took over the lab. He identified the

problem areas and set to work. Training and continual evaluation helped overcome the problem of technician-to-technician variation. So too did restricting the number of technicians who undertook any specific test. Better maintenance and calibration almost eliminated the instrument-to-instrument variation. The blind controls displayed a level of variation only marginally above the limits of the technology in use. Until better technology is introduced, it is difficult to imagine any further improvement.

In another excellent lab, every test had an "owner" who trained all new technicians and who was responsible for maintenance of the equipment, including calibration. This "owner" was the sole authority for his particular test. No changes to sampling, preparation or testing could be made without the "owner's" approval. This methodology, aided by data from blind controls and hierarchical studies resulted in very high levels of precision that approached the limits of the technology. For a lab, this surely is the definition of excellence, where multiple people and instruments can produce a degree of precision that is very close to that achieved by a single instrument with a dedicated, skilled technician. It can be done. It has been done. It will be done again.