NEW ENGLAND PDA NEWSLETTER

30 Jan 08 Volume 3, Number 1

Connecting People, Science and Regulation

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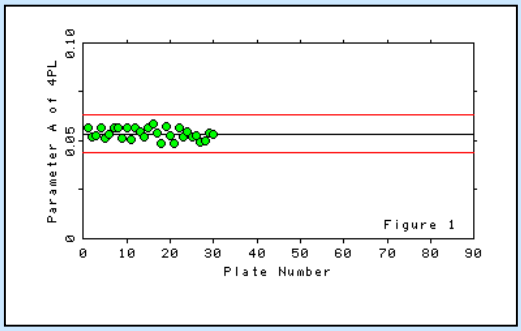
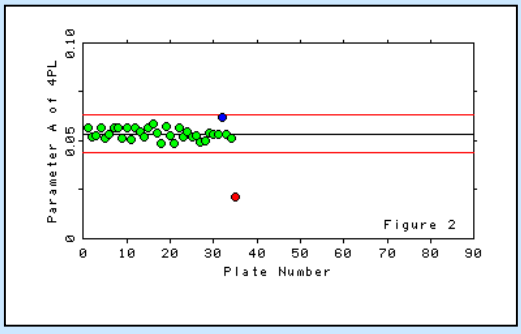
Figures 1 and 2





Trending, Statistical Process Control and Continual Validation

By Stanley N. Deming, PhD, Principal Consultant
www.statisticaldesigns.com

Many researchers are familiar with the graphical technique of "trending" – plotting routine data in sequence to confirm constancy, or to discover unusual events if they occur. As Smith [1] has pointed out, trending helps answer questions such as, "is the [process] still behaving as it was intended ..., has there been a drift, to what could this be attributed, and how can it be addressed?" Although trending has been used most often to monitor manufacturing processes, it can also be used to monitor measurement processes. As an example of this second application, I would like to discuss statistical aspects of trending in the context of bioassays that utilize four-parameter logistic (4PL) models.

When statistics are added to trending, the result is a statistical process control (SPC) chart. Adding the statistical layer helps researchers ignore events that should probably be ignored and pay attention to events that might be important. There are many types of SPC charts, but perhaps the most useful charts for bioassays are the "XmR" charts – individual values (X) and moving range (mR) charts [2].

Following Shewhart's [3] recommendation, confidence limits (plus and minus several standard deviations, or "sigmas") are calculated after about 20 or 30 pieces of data have been accumulated. The upper and lower control limits on individual measured values are easily calculated [4].

Figure 1 shows the center line (black) and the upper and lower statistical process control limits (red) calculated for parameter A of the 4PL model for the reference standard curve after the first 30 plates have been run for a developed and validated bioassay. If the bioassay remains stable with time, then almost all of the future data points are expected lie between the upper and lower control limits.

In Figure 2, five additional bioassays have been recorded. Although the blue data point in Figure 2 is an extreme high data point, it has not gone beyond the upper control limit and thus can be ignored – it is simply "part of the system" and represents nothing unusual. In contrast, the red data point is below the lower control limit and

represents a "three-sigma" rule violation. Something is quite different now, and warrants a closer look. [Note that this is not necessarily an "out of specification" (OOS) event. Specification limits are not related to statistical process control limits. Specifications should be based on practical considerations related to fitness for use, not on statistical descriptions of past events. Don't confuse control limits with specification limits. Control limits should never be used as specification limits.]

Figure 3

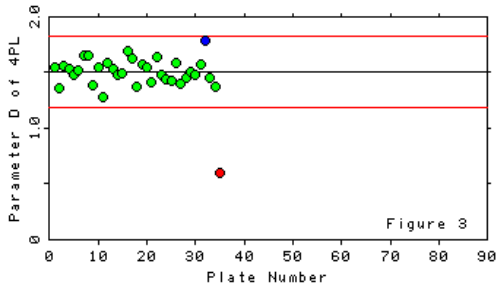


Figure 4

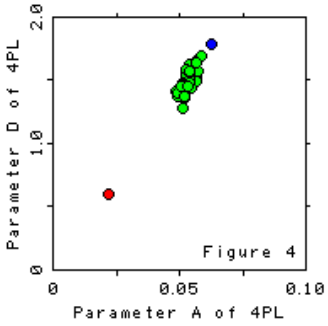


Figure 5

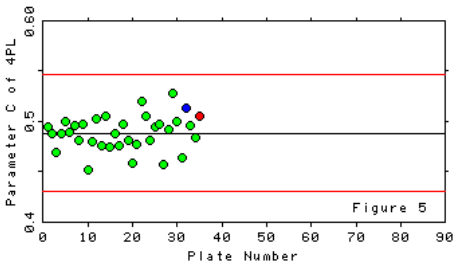


Figure 3 plots a different parameter (the upper asymptote – parameter D) as a function of plate number. Note that the blue data point is an extreme high value, and the red data point is a lower "three-sigma" rule violation. With these two trending charts in front of us, our eyes begin to detect the hint of a correlation between the parameters A and D.

This suspected correlation is confirmed in Figure 4, where parameter D is plotted against parameter A. (Figure 4 is a separate correlation plot, not an SPC chart.) Such correlations between model parameters often exist in bioassays. One common reason is that the measured response depends not only on the amount of pharmaceutical being determined, but also on the amounts of other reagents in the wells; if there is a "top-well" pipeting error in a critical reagent, and it is diluted proportionally "down the plate," all of the wells can be affected, and the results will show up in the estimates of the upper and (perhaps) the lower asymptotes of the 4PL model

One of the major strengths of bioassays is that proportional errors will often cancel out. Figure 5 plots the C parameters estimated for these plates. Interestingly, although the A and D parameters show unusual behavior for the blue and red data points, there is nothing unusual in the estimated values of C for these plates. It is for this reason that I prefer to base "system suitability criteria" (SSC) on critical (but less fragile) parameters like C (or better, on the relative potency of a control sample measured against a reference, where additional errors can cancel out), rather than on less critical parameters like the lower and upper asymptotes (the A and D parameters)

Another behavior that is a cause of concern is "drift," a slow change in the performance of a system. Statistical process control charts are especially good at picking this up with a "rule-of-eight" (I prefer a "rule-of-ten") which detects eight (or ten) or more data points in a row on the same side of the center line. Such a rule violation can be seen in Figure 6, where the ten yellow data points are all above the center line. This is highly improbably behavior, and should be investigated to try to find the source of the drift and correct it before the bioassay becomes unusable. Perhaps in this example a reagent is going bad and needs to be made up fresh.

Figure 7 shows the statistical process control chart for parameter A after a total of 89 plates have been run. It is clear that we have been monitoring the assay and have been aware of unusual behavior (witness the red and yellow points), we have taken actions (or not taken actions) accordingly, and have kept the process in a good state of statistical control.

Figure 6

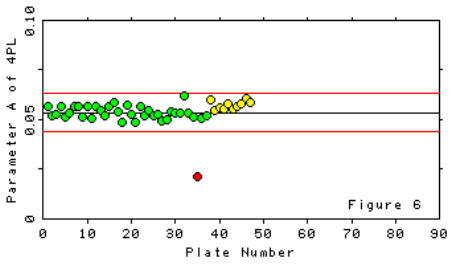
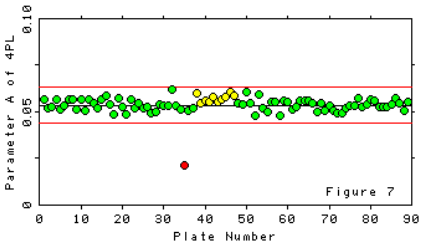


Figure 7



SPC charts are invaluable for making business decisions based on current information: initial validation might provide a "snapshot" of what the assay was doing in the past, but SPC (trending) charts "show the whole movie" of how it has behaved since [1]. Finally, SPC charts are a powerful tool for showing auditors the continual validation of an assay.

References:

[1] Smith, M., "If Method Validation Is A Snapshot, Let's See The Movie," *NEPDA Newsletter*, **2**(2), pp. 4-5 (2007).

[2] Wheeler, D., *Understanding Variation: The Key To Managing Chaos*, SPC Press, 1993.

[3] Shewhart, W. A., *Statistical Method from the Viewpoint of Quality Control*, The Graduate School, The Agriculture Department, Washington, DC, 1939.

[4] Wheeler, D., "Good Limits from Bad Data (Part I), *Quality Digest*, March 1997 (http://www.qualitydigest.com/march97/html/spctool.html).

PRESIDENT'S MESSAGE: January 2008, By *Louis Zaczkiewicz, NEPDA President*

2008 brings in another great year of activities for your New England PDA Chapter (NEPDA). Since our last newsletter in November 2007, we have added tentative plans for two of the events. On September 17 (changed from September 10 due to a conflict with another PDA event) we will have a meeting on the newly released TR43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing. On November 12 our meeting will be on TR29: Points to Consider for Cleaning Validation. The locations are still to be determined, but we hope one of them will include a tour of the Wyeth Andover facility.

We have started a new Science Fair committee headed by NEPDA Past-President, Mark Staples. This spring, the NEPDA Science Fair committee will judge the student entries and select the best three that align with the PDA mission element of promoting advances in pharmaceutical and biopharmaceutical science. The winners will receive monetary awards from the NEPDA and will be invited to display their presentations at a NEPDA meeting. Just before the November meeting, the NEPDA met with officials at Middlesex Community College to develop the PDA's first Student Chapter! We have started a new NEPDA Student Chapter committee headed by NEPDA President-Elect, Jerry Boudreault. As we help develop this new chapter, we hope to help place the students in their Biotechnology program and assist with their needs. Their facility could use donations of scientific equipment to help enrich their students' education. For example they need balances and a couple of 3 liter bioreactors. If you can help with donations or are interested in learning more about placing MCC students, contact Jessie Klein at KLEINJ@middlesex.mass.edu, Jerry Boudreault at boudreault@ddres.com or me.

Best wishes for a wonderful New Year

Louis T. Zaczkiewicz - NEPDA President - zaczkiewicz@pdachapters.org

Middlesex CC Launches Student Parenteral Drug Association (PDA) Chapter

By Jessie Klein, Ph.D., Associate Dean Math and Science, and Jerry Boudreault,NEPDA President Elect

Middlesex Community College, with campuses in Bedford and Lowell, Massachusetts is starting a student chapter of New England Parenteral Drug Association (PDA). Since 1990, the college has offered degree and certificate Biotechnology Technician programs which prepare students for career employment in the biotechnology industry as well as for transfer to bachelor's degree programs. The curriculum emphasizes both an academic and a practical approach.

Students use scientific methods and computer technology to develop medical, food and drug products and will get lab experience and internships at local biotech companies. Many students complete the one-year certificate program, obtain a job in the industry, and return to school, while employed, to complete the associate degree program.

Two Middlesex biotechnology students recently won Community Scholar Academic Scholarships from Boston University's Metropolitan College, joining an impressive number of graduates of MCC's Biotechnology Technician program now studying at BU. Much of the credit for student success goes to Mariluci Bladon, coordinator of the program. Bladon, a native of Brazil who received her doctorate in human genetics from the University of Michigan and did post-doctoral work at Harvard, spent 10 years in the biotech industry before establishing the program at MCC in 1990. Her students receive the training and knowledge that results in virtually 100 percent placement, with many of them enrolling in BU and Northeastern to complete their studies.

In addition to MCC's continued support, Bladon said two factors have been integral to her program's success. One is the Biotechnology Advisory Board, made up of industry professionals who help to monitor changing needs within the field. For example, in October, Bladon instituted a new Embryonic Stem-Cell Project with three honor students who will work with mouse cells.

Her program's other success factor is the internship component, which places MCC biotech students with companies such as , Bladon explained. "Boston is a prime job market for life sciences graduates because of the concentration of organizations involved in pharmaceuticals, biotechnology, medical devices and research and development. When our biotech students graduate, they are ready to work. Often, their new employers pay for their continuing education" Bladon said.

"We are very pleased about our collaboration with MCC", said NEPDA President Elect, Jerry Boudreault. "MCC has a great track record of preparing their students for challenging positions in the local health sciences industry. It represents a wonderful opportunity for our members to get involved in helping to develop the workforce of the future".

Interested students will be provided with PDA Student Membership which entitles them to receive publications such as the PDA Journal and Technical Reports as well as attend PDA educational programs and other networking opportunities at a discounted student member rate. NEPDA will fund the program as well as provide MCC with speakers on topics of special interest. We will also solicit our members for donations of equipment and supplies on behalf of the program. Surprisingly, a significant portion of the supplies and equipment used by the program comes from donations from local companies.

The possibilities are limited only by our creativity. If you would like to participate in the MCC Student Chapter contact Jerry Boudreault at Boudreault@ddres.com.

Connecting People, and Regulation

The New England Chapter of the PDA is pleased to announce the ***availability of advertising opportunities in our newly launched newsletter.*** Since its inception in 1988, our chapter has seen a significant growth in membership and participation. Our newsletter has the following reach:

- Our direct e-mail distribution reaches over 1,200 contacts throughout New England.
- Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, regulatory, ***etc.***
- The newsletter is promoted at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.
- The newsletter is posted to our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.

We offer vendors, consultants, operating companies and other organizations the opportunity to promote themselves and also support the NE PDA Chapter by purchasing advertising in our newsletters

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TECHNICAL NOTE

Bubble-Free Filling® Promotes Product Sterility

By Kelly Lin, Editorial Specialist, HCM, from presentation by Dr. Shawn Kinney, president of HCM, at the Universe of the Prefilled Syringe Show in Berlin, Germany,
www.hyaluron.com

Freedom of stopper movement in a prefilled syringe, when coupled with a sizeable gas bubble can potentially cause significant challenges to product sterility and package integrity when a syringe is exposed to changes in atmospheric pressure, such as can occur during shipping at higher elevations.

In a syringe, a sterile barrier is created while the stopper is in contact with the barrel of the syringe. The height of the sterile barrier, or $H_{sb,}$ represents the maximum distance a stopper can move—either in a single episode, or as the result of several up and down movements—before potentially contaminating the product.

A gas bubble inside a syringe acts like a spring, expanding and contracting with changes in ambient pressure. As ambient pressure decreases, the bubble—which is not intrinsic to the syringe but is the result of conventional filling processes--expands, causing the stopper to move into non-sterile areas of the syringe barrel. As pressure returns to its original levels, however, the stopper returns to its original position, potentially pulling contaminants into the drug product.

A recent study conducted by Hyaluron Contract Manufacturing (HCM) found that the amount of stopper movement which results from changes in pressure is proportional to the size of the gas bubble inside the syringe and can be predicted by a theoretical calculation using Boyle's Law. One way to protect product sterility during shipping, the study concluded, is to reduce the size of the bubble. According to the study findings, the maximum allowable size of a gas bubble can be calculated using the height of the sterile barrier ($H_{sb)}$, the pressure differential to which a syringe will be subjected, as well as the number of times which a syringe will undergo changes in atmospheric pressure. (see figure 1)

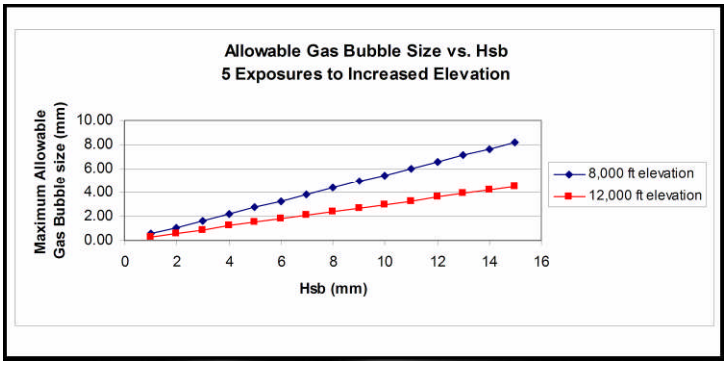

Figure 1. This data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 $H_{sb.}$