Tom Layloff

Parametric Release In Lieu of Drug End-Product Testing: Can We Get There From Here?

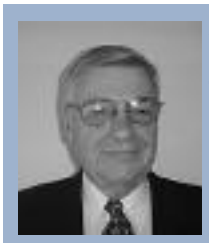
In the mid-1980s, the U.S. FDA accepted parametric release (PR) of sterile products in lieu of end-product sterility testing.* This formal adoption of a totally Good Manufacturing Practices (GMP)-based product release or PR was driven by several interesting constraints. First, the desired sterility acceptance level of no more than ca. one sterility unit failure per million units posed an extraordinary sampling issue when one considers that a batch of product could consist of only 500,000 units. Second, the USP sterility test sampling model is capable of detecting sterility failures of greater than about 15%. These constraints made the concept of end-product release sterility testing to ensure compliance untenable. The only viable and scientifically valid option to ensure compliance with the desired quality standard was to develop and validate surrogate process performance criteria for the critical process control points. In this surrogate validation model, samples with known levels of contamination are subjected to defined temperature and pressure levels to establish microorganism load reductions that could be expected to extrapolate to actual products.** It should be noted that this sterility assurance model uses a surrogate validation model with process analytical technologies (PAT) that are not directly related to end-product sterility testing, e.g., the validation data establish, through alternate assessment tools and strategies, an implication that the end-product testing sterility requirement will be met.

Similar parametric sterile product release strategies are also employed for vaccines and other products in which the defect acceptance levels do not make end-product sampling and testing a viable option. For vaccines, consider that last year ca. 87 million flu vaccinations were delivered, and that states require almost universal well-child vaccinations, e.g., Illinois requires nine vaccinations each for over 200,000 well children who annually begin attending schools or day-care facilities. With products such as these, even a few percent of nonsterile product would be disastrous. A similar problem exists for the determination of aflatoxin contamination in peanuts. The FDA regulations for raw peanut lots specify a 25-ppb aflatoxin action level. For a 20-ton lot of peanuts, that limit would be exceeded if ca. 0.5 g or one-third peanut equivalents of the approximately 1.2×10^7 peanuts in the lot were present as aflatoxin. This example also poses an interesting sampling problem: How does one obtain a representative analytical portion to determine if a box car full of peanuts will meet the limit—or find a needle in a haystack?

continued

*The U.S.FDA states: "Parametric release is defined as a sterility release procedure based upon effective control, monitoring, and documentation of a validated sterilization process cycle in lieu of release based upon end-product sterility testing (21 CFR 211.167)." The Pharmaceutical Inspectional Cooperation Scheme (PIC/S) model of parametric release of sterile products is posted at www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate, and the European Union parametric release document CPMP/QWP/3015/99 is available at www.emea.eu.int.

**It is estimated that these validated processes reduce the microbiological load by 6–13 logs or 10^6–10^{12} times.



Dr. Thomas Layloff *is Principal Program Associate in the Center for Pharmaceutical Management, Management Sciences for Health (MSH, www.msh.org) addressing pharmaceutical quality issues in international commerce and developing nations, and Adjunct Professor of Chemistry, St. Louis University (Missouri). He also serves as a Special Government Employee in the U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) as the Acting Chair of the Pharmaceutical Analytical Technology Subcommittee (PAT). PAT is an advisory to CDER in the development of a guidance document that will address the incorporation of new technologies into the approval processes. Prior to joining MSH, Dr. Layloff was employed by the United States Pharmacopeia (USP) as Vice-President and Director of the Pharmaceutical Division (Rockville, MD). He has also served as Associate Director for Standards Development (CDER, Rockville, MD) and for over 20 years as Director of the FDA's leading pharmaceutical testing laboratory (St. Louis, MO). He was elected to the USP's Committee of Revision where he served as a member of two Chemistry Revision Subcommittees, Chair of the General Chapters Subcommittee, member of the Reference Standards Committee, and member of the Division of Standards Development Executive Committee (policy-setting body for USP standards) and its Chair. He is very active in the FDA and California Separation Science Society jointly sponsored WCBP (formerly the Well-Characterized Biotechnology Pharmaceuticals) symposium series, where he served/serves as Co-Chair of the 2001, 2002, and 2003 meetings, and as member and past-Chair of the Permanent Organizing Committee (www.casss.org). He is Past-President and Fellow of AOAC International, and Fellow of the American Association of Pharmaceutical Scientists. He is a member of Sigma Xi and Phi Lambda Upsilon honorary societies. He received BA/BS degrees in Chemistry and an MS in Organic Chemistry from Washington University (St. Louis, MO), and a Ph.D. in Analytical Chemistry from the University of Kansas (Lawrence).*

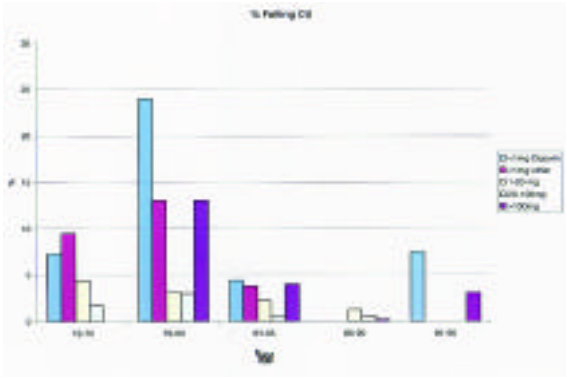


Figure 1 *Tablet and capsule relative standard deviations.*

The strikingly successful sterility PR and PAT applications model broaches the issue as to whether these concepts can be applied more broadly to other FDA regulated products. In other industries, it has long been known and accepted that PR and PAT can be used effectively to provide a very high level of assurance of product quality, i.e., PAT can help ensure that quality is built into the process; end-product testing generally does not allow a ready option of recovery into compliance for that lot of product.[1–4] As in the sterility release model, there are many other instances in which a higher level of product quality assurance can be achieved through surrogate validation schemes than direct end-product measures.

The manufacture of pharmaceutical products poses an interesting PR challenge. In the pharmaceutical discovery process, analytical technologies are developed to assess the impurity levels so that they can be properly controlled. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[a] qualification limits for active pharmaceutical ingredients (API) impurity levels of ca. 0.1% or one part per thousand (ppt) are typically conducted using high-performance liquid or gas liquid chromatographic (HPLC or GLC) methods. These assessment tools are the keystone of the discovery efforts and frequently move with API through phase 1 to phase 2 product development assessment strategies. More interestingly, these discovery assessment tools are frequently incorporated into the process control assessments, where chromatographic assessments of the API, as in blend uniformity assessments, are used as the surrogate marker for the quality of the manufacturing process. These chromatographic assays are employed for these process control assessments even in instances where the processing will not appreciably change the API impurity levels. Although in many instances there are alternative assessment tools or PAT, which with appropriate surrogates could provide better process performance endpoints, these are not frequently used in the highly regulated pharmaceutical industry for several reasons.[b] Many of these assessment technologies provide a higher level of product quality consistency within the context of statistical repeatability and reproducibility than do the repeated API-based chromatographic assessments. In addition, there are numerous instances in which the uniformity of the API alone did not ensure product performance because of inappropriate distribution of other components in the formulation. There are even more examples in which the application of these API surrogates has resulted in inefficiencies and higher costs because of process delays.

Although the quality of solid dosage form products may have been based on inefficient end-product testing protocols,[c] there has been a remarkable improvement in product consistency over time. This industry-wide quality improvement likely arose due to increased FDA enforcement and more strict GMP oversight. These observations were presented in a publication that summarized content uniformity testing of almost 11,000 samples of single component tablets and capsules conducted by the FDA from 1972 to 1995.[5] The relative standard deviation (RSD) data presented in a bar chart in *Figure 1* were grouped by time periods 1972–1975, 1976–1980, 1981–1985, 1986–1990, and 1991–1995. In general, the RSD decreased with increasing dosage level and with time periods from 1976–1995. For some unknown reason, the data for the time period 1972–1975 for low dose samples are lower than for the subsequent period from 1976 to 1980. For that time interval, 214 (13.5%) of 1582 samples of digoxin (DIG), digitoxin, and nitroglycerin (NITRO) products were found with a high RSD. For other active ingredients, the following results giving the percent of samples with high RSD were obtained: less than 1 mg—4.0% of 840 samples, 1–20 mg—2.0% of 2545 samples, 20–100 mg—1.1% of 3292 samples, and greater than 100 mg—0.6% of 2461 samples.

These observations are consistent with an API-based surrogate process quality assessment mode; higher API percentage formulations have lower failure rates. The ICH qualification schemes at the one ppt level along with chromatographic assessments typically exhibiting RSDs in the low percent range do not pose a repeatability/reproducibility issue for the assessments of assay limits of 90–110% and content uniformity limits of 85–115%. However, the application of univariate surrogate quality assessment models to ensure polyvariate process performance endpoints is technically marginal.

In the process variance budget, the initial weigh-in of the formulation components is probably the smallest factor; balance accuracy has a variance in some instances of less than one part per million (0.00001 in weighing ca. 10 g).[d] The use of univariate API chromatographic assessment tools to monitor process controls and performance endpoints adds variance at the percentage level, and these contributions likely dominate the end-product variance. Looking at the quality of the manufacturing pro-

[a] See www.ifpma.org for details.
[b] See the meeting agenda for the "Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science," Feb 25–26, 2002, Gaithersburg, MD. www.fda.gov/ohrms/dockets/ac/02/agenda/3841a1_revised.htm.
[c] End-product testing is sometimes used to release product for marketing, although the analytical portion has not been demonstrated to be representative of the lot and the lot itself has not been assessed to establish an appropriate mathematical representation that could be used to establish a statistically appropriate sampling plan to ensure that a valid analytical portion is obtained.
[d] For examples, see www.mettler-toledo.com.

cesses using other PAT assessment tools such as near-infrared (NIR) absorption spectroscopy, which "sees" chemical bonds of all components; Raman and laser-induced-fluorescence (LIF), which "see" emission from many molecules; and acoustic detectors, which "hear" the processes, offer strikingly better approaches to assess in-process consistency and improved performance-based process endpoints.

The FDA Center for Drug Evaluation and Research (CDER) initiative to develop guidance documents to encourage the submission of marketing applications that include PAT-based assessment technologies should be helpful in aiding the regulated industry to appropriately employ more efficient polyvariate assessment tools that will provide a higher level of assurance of product quality in addition to reducing the cost of product quality assurance. The regulated industry should aid in the development of this guidance document by bringing forward examples in which these PAT can be successfully validated.

It's a brave new world out there and we *can* get there from here. The cGMP regulations are sufficiently broad to allow these innovations to be adopted into performance-based process endpoint assessments.

References

1. Workman Jr. J, Creasy KK, Doherty S, et al. Process analytical chemistry. Anal Chem 2001; 73(12):2705–18.
2. Workman Jr. J, Veltkamp DJ, Doherty S, et al. Process analytical chemistry. Anal Chem 1999; 71(12):121–80.
3. Blaser WW, Bredeweg RA, Harner RS, et al. Anal Chem 1995; 67:47R–70R.
4. Beebe KR, Blaser WW, Bredeweg RA, et al. Anal Chem 1993; 65:199R.
5. Wells CE, Layloff TP. Retrospective summary of twenty years of content uniformity data for tablet and capsle dosage forms. Pharmacop Forum 1997; 23(4):4583–6.

AG/PT