REGULATORY FOCUS

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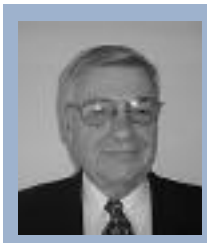
Is It Time to Move On?

*"[T]his irresistible revolution that for so many centuries has marched over all obstacles, and that one sees still advancing today . . ."**

The production of therapeutic agents began with compounding physicians and pharmacists, who weighed, ground, packaged, stored, and dispensed them. Historically, the therapeutic agents were mineral, plant, and/or animal products whose purported efficacy was established through folklore. Many of these folkloric products dropped from use because of ineffectiveness and, in some instances, toxicity, but many also withstood the efficacy test of time and eventually evolved into products such as digitalis leaf to elixirs and thyroid gland to defatted and desiccated glandular material. Improvements in standardization of these products over time led to more widespread and safer use of the agents. With the advent of improved chemical separation techniques, these materials yielded chemically defined therapeutic agents, e.g., digoxin, reserpine, levothyroxine sodium, and insulin, which could be better quantified and dispensed. With the advancements in separation techniques and chemical synthesis, the sources of therapeutic agents began to move to the chemical reagent shelves. Further scientific and technical advances have brought biochemical syntheses of new classes of therapeutic agents as well as new routes to traditional agents, such as insulin, in genetically modified bacteria, insects, mammals, and plants.

With this evolution from natural sources to natural-source derived products to reagent shelves to fermentation isolates, there has been some evolution in production and process quality. However, there has been limited advancement in the technologies used to assess and control process quality. Our very successful pharmaceutical industry is conservative with regard to changes beyond the drug discovery processes. In the drug discovery domain, we find a feverish search and high levels of automation implementation such as high-throughput screening, along with innovative technology applications such as elegant receptors–donor interaction simulations in product design, and organizational development. However, in the midst of this discovery process revolution, there has not been a corresponding revolution in the processes and process control assessment technologies. Pharmaceutical manufacture and process quality assessment technologies have lagged far behind the discovery technology innovations. Many processes, e.g., time-release

*Emphasis added by author. de Tocqueville A. Democracy in America, translated by Mansfield HC, Winthrop D. Chicago, IL:University of Chicago Press, 2000:5.



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bead coating, are still conducted manually or with technology approaches dating back half a century. The manufacturing side of the pharmaceutical industry has not moved to exploit the opportunities offered by the information revolution as have, for example, the automobile and oil industries.

The reasons for this lag no doubt are multifaceted, including "If it ain't broke, don't fix it," "Using new technologies may present new knowledge and thereby pose new regulatory issues," and the U.S. FDA investigators will have problems understanding the technology and cite more adverse findings. With the historical outstanding financial performance in the industry, it is easy to understand the first point; the industry obviously "ain't broke," at least financially, at this time. With regard to the latter two points the U.S. FDA, primarily through the lead of Dr. Ajaz Hussain, Deputy Director for Science in the Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Science (Rockville, MD), is attempting, with assistance from the Advisory Committee for Pharmaceutical Sciences, to address these issues. Dr. Janet Woodcock, Director, CDER, and Dr. Hussain gave presentations on this subject recently to the U.S. FDA Science Board, and their presentations were summarized in the Executive Summary (www.fda.gov/oc/advisory/execsumm040902.html) as follows:

> Dr. Woodcock discussed the steps to proceed forward in the process analytical technologies area (as presented at the November 2001 meeting). She suggested that some of the concerns of manufacturing problems while introducing PATs [Process Analytical Technology] are from perceived regulatory oversight and the implication of FDA looking more closely at manufacturing processes. Innovation and investment in the manufacturing sector is being driven by enforcement and compliance activities of the Agency, rather than by the use of science-based approaches for processing. Dr. Woodcock solicited the Board's opinion on the FDA's presented strategies for working with the pharmaceutical companies to address this concern.
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> Dr. Hussain outlined the FDA's proposed process and timeline for addressing the issues and explained that the PAT initiative serves as a model, and as an opportunity to develop a regulatory frame work to facilitate introduction of new manufacturing technologies for more efficient processes. He outlined the key objectives including eliminating perceived or real regulatory hurdles; developing a CDER-ORA team based approach for regulatory review and inspection; and, international harmonization. The PAT model moves from the current "testing to document quality" paradigm to a "continuous quality assurance" paradigm.

The noted continuous quality assurance (CQA) paradigm will improve the quality of drug products by providing a more thorough assessment of a production run. This improved process control will improve product quality and reduce recalls and production dwell time and thereby improve production efficiency. The current assessment paradigm is based on process quality assessments using end-product testing technologies on portions of a production lot.* With regard to the uniformity of products, the USP has an interesting duality in the testing protocols for the uniformity of dosage unit (<905>), which states:

> Unless otherwise specified in the monograph, the requirements for dosage uniformity are met if the amount of the active ingredient in each of 10 dosage units as determined from the Weight Variation or the Content Uniformity method lies within the range of 85.0% to 115.0% of label claim and the Relative Standard Deviation is less than or equal to 6.0%.
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> If 1 unit is outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, or if the Relative Standard Deviation is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim and the Relative Standard Deviation of the 30 units does not exceed 7.8%.

In this monograph, the USP mixes with its usual pass–fail attribute testing model, a population testing standard, i.e., no unit outside a defined window *and* a standard deviation limit. The imposition of both standards presents an interesting conflict. If one assumes a normal distribution for a production lot of one million tablets with a mean content of 100%, which meets the USP content uniformity (CU) relative standard deviation (RSD) limit of 6%, the probability of the batch passing the stage one test is 0.957; the probability of failing is then 0.043. However, the passing 95.7% and failing 4% are both from the same statistical population. Further, the USP attribute limit model requires that no tablet be outside 75.0% to 125.0%, although statistically in the 6% RSD batch cited above, there would be 30 tablets outside that limit and 12,419 tablets outside the 85.0% to 115.0% window.** In a 100% product quality assessment model, a batch could meet the 6.0% RSD limit but would fail the no tablet outside the 75.0%–125.0% test. It is interesting to note that the statistically valid sampling paradigm that CQA would bring raises the specter of more failing batches because of units outside the 75.0%–125.0% limits. In order to avoid this dilemma, it will be necessary to assign a CU RSDquality assessment standard for the CQA paradigm. However, the USP pass–fail attribute assessment paradigm is appropriate for marketplace testing because a statistically valid sample is not available.

To this author's knowledge, there has been over the past 25 years or so

*The USP requires testing 10 tablets for content uniformity. Generally, this number is not obtained by a statistically validated sampling protocol and the sample lot generally has not been shown to be represented by a normal distribution. However, the USP makes no claim of statistical validity for this marketplace testing model.

**These data are taken from slide presentations to the FDAScience Board Update, "FDA Regulation of Drug Quality:New Challenges," Janet Woodcock, M.D., April 9, 2002, and from the update to the May 8, 2002 Advisory Committee for Pharmaceutical Science Meeting, "The Process Analytical Technology (PAT) Initiative:Progress Report and Next Steps," Ajaz Hussein, Ph.D.

a dearth of reported therapeutic failures due to CU for products that met the USP limits. This marketplace test of the standard indicates its suitability to ensure safety and efficacy, and there is little justification for tightening the window regardless of the CQA assessment technologies implemented.* An RSD-based assessment limit would be appropriate for CQA, while the pass–fail paradigm should be retained for marketplace testing.

To help advance the implementation of PAT and CQA while reducing the perceived regulatory burden, the U.S. FDA is planning to issue a series of guidance documents to facilitate the submission for approval of new technologies to improve manufacturing efficiencies and reduce product defects. With regard to the last concern cited above, the CDER is hiring scientists who are expert in sensor technology and process engineering to assist in reviewing submissions that include these newer technologies. In addition, the CDER is developing, in concert with several universities, a training program for a group of Chemistry, Manufacturing, and Controls (CMC) review scientists and FDA investigators who will provide the nucleus to facilitate the U.S. FDA's regulatory transition to these new technologies. This cadre of specially trained process analytical technologies regulatory staff with assistance from technology experts will review incoming submissions for approval using PAT assessment technologies and strategies, and the PAT-trained reviewer–investigator teams will perform the inspections of those processes. This initial trained group will be the harbinger of a cadre of other trained U.S. FDA personnel performing the review and inspections of PAT and other high-tech processing and process-control quality assessment systems.

Because the common concepts of validation tend to be tied to chromatographic procedures with a well-behaved detector, process endpoint signatures will present interesting validation challenges and even more striking data storage and retention challenges. Product homogeneity endpoints assessed by image detection bring interesting assessment strategies, which we constantly address in other contexts; the stew looks stirred well enough and uniform to go to the table. Near-infrared, Raman, and laser-induced fluorescence almost cross over into the traditional mode until the endpoint is defined as a signature or fingerprint covering a wide spectral region with acceptance based on a spectral deviation window. The implementation of these CQA–PATs will pose challenging 21 CFR 11 record definition and retention issues; some of these issues will be the subject of future articles.

The "irresistible revolution" in information-based assessment technology is upon us, and it will be important for the industry to encourage the U.S. FDA to continue to pursue these programs to help speed their implementation to bring better quality pharmaceuticals to the marketplace. It is anticipated that the inclusion of more modern technologies will reduce production costs and ultimately consumer costs. **AG/PT**

"TO HELP ADVANCE THE IMPLEMENTATION OF PAT AND CQA WHILE REDUCING THE PERCEIVED REGULATORY BURDEN, THE FDA IS PLANNING TO ISSUE A SERIES OF GUIDANCE DOCUMENTS TO FACILITATE THE SUBMISSION FOR APPROVAL OF NEW TECHNOLOGIES TO IMPROVE MANUFACTURING EFFICIENCIES AND REDUCE PRODUCT DEFECTS."

*Most drug products have a wide therapeutic window, i.e., the range between therapeutic effect and toxicity is wide on a percentage basis, which minimizes the effects of CU. Also, many drug products have a relatively long half-life in the body, which helps to average the CU variation.