FDA'S INITIATIVE ON PHARMACEUTICAL QUALITY SYSTEMS FOR THE 21ST CENTURY AND THE DEBATE ON DELIVERED DOSE UNIFORMITY FOR INHALERS

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The opinions expressed in this paper are those of the author and may not necessarily represent the views and policies of the FDA.

KEYWORDS:

SUMMARY

This paper provides a brief overview of FDA's Pharmaceutical Quality for the 21st Century Initiative and explores the relationship of that initiative to the protracted debate between FDA and industry on DCU specifications for inhalation products. The IPAC-RS proposed PTIT is generally agreed to be a better alternative in many respects to the current FDA DCU test, but significant issues remain to be resolved. The FDA's 21st Century Initiative provides an excellent framework for resolving these and future issues efficiently, by bringing together scientists responsible for product development, production, quality assurance, and regulatory review and inspection with the goal of ensuring product quality using up-to-date concepts of risk management and quality systems.

INTRODUCTION

Quality pharmaceuticals prevent and/or cure diseases, alleviate suffering, extend life, and improve quality of human life. Availability, which encompasses the notion of affordability, of these products is essential for individual members of the population and for the growth and prosperity of any nation. Societies around the world provide a varying degree of regulatory oversight on the functions of the pharmaceutical industry: to ensure truthful therapeutic (safety and efficacy) claims and quality standards commensurate with each product's intended use. Most regulatory decisions are risk-benefit decisions that have to conform to societal directives expressed in statutes and regulations. Effective and efficient regulatory practices are essential for realizing a society's public health objective.

Over time, regulatory requirements generally increase in response to real and perceived inadequacies of risk coverage. This increases system complexity and the demand on sparse resources for ensuring compliance. Increasing system complexity makes it challenging to maintain the overall coordination and connectivity of risk coverage and to evaluate system effectiveness and efficiency. Moreover, without the ability to evaluate effectiveness and efficiency of the regulatory procedure, it is difficult to ensure appropriate risk coverage and continuous system improvement.

A general societal expectation is that a nation's public health objective is best served with regulatory standards that are based on contemporary scientific and risk management principles. The process of ensuring that contemporary scientific and risk management principles are the basis for regulatory practice should be an integral part of an organization's continuous improvement program. Without such a program, the system can stagnate and lose its ability to ensure optimal risk coverage, hinder modernization, and adversely influence the efficiency of the regulated industry.

The practice of pharmaceutical development and manufacturing continues to evolve with increasing emphasis on science and engineering principles. However, significant opportunities exist today for improving the quality and efficiency of pharmaceutical development, manufacturing, and quality assurance; this through the application of modern product and process development principles, process analytical chemistry and control tools, and contemporary quality and risk management principles.

The pharmaceutical industry generally has been hesitant to introduce new technologies and innovative systems into the manufacturing sector for a number of reasons. A reason often cited is *regulatory uncertainty*, which is often a perception, based on unfavorable interactions with a regulatory system, that the existing regulatory system is rigid and restrains introduction of new technologies. Hesitancy in the current regulatory system (derived from both industry and FDA) to broadly implement modern manufacturing principles and technologies is undesirable from both public health and business perspectives.

The FDA's Process Analytical Technology (PAT) initiative launched in July 2001 is intended to ensure judicious regulatory utility of, and support for, advances in pharmaceutical science, engineering, quality systems approaches and technologies to enhance manufacturing quality and efficiency (1). Under this initiative, specific steps were undertaken to identify and address *regulatory uncertainty* associated with the introduction of new technologies in pharmaceutical development and manufacturing. The PAT initiative was followed, a year later, with a broader initiative on Pharmaceutical CGMPs for the 21st Century (2). This initiative is not just about CGMP inspections but covers the entire regulatory pharmaceutical quality process; it also includes CMC product review aspects. Therefore, it is often referred to as the Pharmaceutical Quality System for the 21st Century Initiative. The PAT initiative is now part of this pharmaceutical quality initiative. Recently, this broad initiative was made an important component of the science-based risk management goal in the Agency's *5-Part Strategic Action Plan to Protect and Advance America's Health,* announced in August 2003 (3).

This paper provides a brief overview of the "Pharmaceutical Quality in the 21st Century Initiative" and examines a very specific issue: the potential link between this initiative and the debate on Delivered Dose Content Uniformity (DCU) specifications for oral and nasal inhalation drug products (ONIDP). To set the stage for this discussion, a hypothetical case study will be used to frame questions that illustrate the important dimensions of the problem at hand.

CMC REVIEW AND CGMP INSPECTION INTERFACE

Using a simplified and hypothetical case (constructed to illustrate some of the features of challenges encountered in certain manufacturing situations), this section will explore the CMC review (e.g., specification setting) and CGMP inspection (e.g., issue of a Warning Letter) interface.

During an inspection of a manufacturing facility, an FDA investigator observed a very high batch rejection frequency (at release and upon stability testing) of an inhalation product with respect to its DCU specification (batch rejection and recall of batches with Out of Specification (OOS) results had occurred). The product had been on the market for more than five years and the observation led to a Warning Letter; the reason cited was "failure to adequately validate the manufacturing process." The company's response to the Warning Letter was a proposal to revalidate the process.

At this juncture, we should ask whether, from a science and risk management (to patient/quality as well as regulatory risk) perspective was this an optimal solution?

For a rational discussion of this case, a series of subsidiary questions should also be asked and discussed. The following questions and comments are some of those which come to mind:

- **What constitutes an OOS result? How does one distinguish such a result from a statistical "outlier"?** The US District Court for the District of New Jersey (Civil Action No. 92-1744) expressed an Opinion that outlier analyses should not be used for chemical assays, because *if they were appropriate, the USP would have recommended the procedure* (4). This opinion suggested the fact that the outlier test in the USP is only directed toward biological assays; because no mention is made of chemical assays, the test (for outliers) was not applicable to chemical assays (5). In practice, the FDA has recognized the need to address "outliers" for any assay in its draft Guidance, *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production* (September 1998) (6).

- **What are the criteria for *high batch rejection frequency*? What is the relationship between this frequency and the state of process control/validation?** The Opinion in the Court case cited above suggests that a rejection of 10% or more of manufactured batches may be considered as *high batch rejection frequency*. However, scientific answers to these questions are long overdue, as is a discussion on the issue of outliers; FDA guidance is needed to clarify this issue. Clearly, the batch rejection frequency is one of the dimensions (*probability*) of risk to quality. This and the other risk dimension, *consequence (or severity of harm),* are discussed below.

- **Since this product was approved and validated before marketing, how many batches were produced before a *high batch rejection frequency* became apparent?**

- **What is the FDA process for detecting *high batch rejection frequency* and communicating this finding within the Agency to ensure appropriate risk assessment and resolution?**

- **What are the consequences of *high batch rejection frequency* for a particular product and what is the estimated risk to quality?**

- What factors (root causes) contributed to the *high batch rejection frequency*?
  - If an *assignable cause* for *high batch rejection frequency* cannot be identified (a frequently observed scenario), what options are available for resolving this dilemma?
  - How does one ensure adequacy of the root cause investigation to be conducted?
  - What data/information was available for the root cause investigation?
  - Does the current system encourage collection of information (other than that available in the batch records), so as to be able to identify root cause?
  - If, for example, one increases the sample size for testing, in order to get a robust estimate of product variance, this may simply increase the probability of rejecting a batch. Moreover, data in batch records pertaining to currently used non-parametric specifications may not provide a means to get a robust estimate of variability. If this is the case, how should we identify relevant sources of variability in a CGMP setting?

- Assuming that the root cause investigation is judged to be adequate, should it be deduced that the product/process design is inherently variable (random variability)? If so,
  - Should it be interpreted that this product/process design is not capable of consistently meeting the set DCU specification?
  - Should the process be revalidated? If so, what will this activity entail?
  - Should the process be improved (reduced variability)? If so, how?
  - Could attempts to address inherent (random) variability, without addressing the basic product and process design, increase the risk of the process truly going out of control?

- Since the risk-benefit decision for the DCU specification and approval were based predominantly on assessment of clinical and CMC data, derived from the clinical batches on the same product/process design, how can this knowledge be used to evaluate risk to quality? (e.g., bring together the consequence of high batch rejection and its frequency/probability)
  - If this case exposes new and significant risk factors, what are immediate and long term action steps necessary to communicate and mitigate this risk?

- What data/information is necessary for this evaluation? (e.g., consumer complaints, AERs, dose-response relationships, development information, etc.)

- If the clinical data, consumer complaint analysis, AERs, and other relevant data do not identify an increased risk (relative to the original approval risk-benefit decision), should the DCU specification be modified?
  - To be consistent with the inherent variability of the approved and validated process (e.g., to minimize unnecessary batch rejections and the need for frequent OOS investigations, so that company and Agency resources can be focused on other more important high risk situations)?

- Alternatively, should the original DCU specification be retained because clinical data, AERs, and consumer complaints are often considered to be insufficiently discriminating to detect the impact of variability in DCU on an individual patient basis?

- If the original DCU specification is to be retained, could this not be considered to be an "arbitrary" public standard? Alternatively, does the high manufacturing cost (low production cycle time due to frequent OOS investigation, batch rejection, recall of released batches, land-fill or incineration costs for disposal of rejected/recalled batches, etc.) provide the necessary

incentive to improve the product/process design? Why is this so, and ultimately, who pays for this inefficiency?

- **What lessons can be learned from these types of cases?**
  - Is the current approach ("one-size-fits-all") to setting specifications an optimal risk-mitigation approach?
  - How should specifications be set to satisfy both clinical objectives and process capability?
  - Would an *interim specification* approach at the time of approval plus a Phase IV commitment to finalize the specification based on process capability data and other relevant supporting data provide an improved manufacturing science approach for preventing these types of problems?
  - What type of pharmaceutical development (particularly, the Manufacturing Controls (the MC portion of CMC) information would be most useful to assess quality by design and establish risk-based specifications?
  - Is the current approach ("one-size-fits-all") to setting specifications a significant hurdle for introducing new non-CFC based inhalation products and novel products? If yes, what information is available to enable FDA to evaluate that the current manufacturing technology is truly not capable of meeting a "one-size-fits-all" standard? Furthermore, how should FDA ensure continuous improvement in technology to minimize risk, improve risk-benefit decisions, minimize multiple CMC review cycles and ensure a timely drug approval process?
  - Was a *Warning Letter* approach the optimal action in this case? The risk-benefit decision during NDA review and approval were based on clinical data derived for the approved product/process design, and as part of this process if the DCU acceptance criteria set conservatively and without considering process capability to minimize concern by ensuring a high rejection frequency and to exclude perceived risks from the marketplace - the high failure rate was by design?
  - What should the Agency do to ensure continuous improvement?
  - Are new procedures necessary to ensure coordinated and synergistic interactions between CMC review and the CGMP inspection process?
  - How do we move from a "testing to document quality" to "quality by design"?

The fundamental premise of our pharmaceutical quality system is that: *quality cannot be tested into products, it needs to be built-in, i.e., it has to be designed.* At the present time, many of the questions posed above are difficult to answer. Therefore, this hypothetical case study, at a minimum, suggests a need for improvement in systems thinking, coordination, communication, and the inception of a team approach between CMC review and CGMP inspection both in FDA and industry.

The above questions also relate to the following discussion on the FDA initiative that was introduced as follows:

"As we approach the 25th anniversary of the last major revision to the drug CGMP regulations, it is time to step back and evaluate the currency of these programs so that: (1) the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality; (2) the latest scientific advances in pharmaceutical manufacturing and technology are encouraged; (3) the submission review program and the inspection program operate in a coordinated and synergistic manner; (4) regulation and manufacturing standards are applied consistently; (5) management of the program encourages innovation in the pharmaceutical manufacturing sector; and (6) FDA resources are used most effectively and efficiently to address the most significant health risks."

DIMENSIONS OF PHARMACEUTICAL CGMP FOR THE 21ST CENTURY

The Pharmaceutical Quality System for the 21st Century Initiative may be described in terms of the following six dimensions:

- Risk-based orientation: To provide the most effective public health protection, FDA will match its level of effort to the magnitude of risk. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.
- Science-based policies and standards: Significant advances in the pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. While this knowledge has been incorporated in an ongoing manner into FDA's approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology and contributes significantly to assessment of risk.
- Integrated quality systems orientation: Principles from various innovative approaches to manufacturing quality that have been developed in the past decade will be evaluated for applicability; CGMP requirements and related pre-approval requirements will be evaluated according to applicable principles. In addition, interaction of the pre-market CMC review process and the application of CGMP requirements will be evaluated as an integrated system.
- International cooperation: The globalization of pharmaceutical manufacturing requires a global approach to regulation. FDA will collaborate with other regulatory authorities, via ICH and other venues.
- Strong public health protection: The initiative will strengthen the public health protection achieved by FDA's regulation of drug product manufacturing and will not interfere with strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.
- Time: This two-year initiative will lay out a framework to realize the goals and objectives of the initiative over a period of time extending beyond the two-years. These goals and objectives are directed for achieving the "desired state" of pharmaceutical development, manufacturing, quality assurance, and the associated regulatory system.

GOALS AND DESIRED STATE

The activities of this initiative to date have been focused on developing projects to (7):

- Encourage the early adoption of new technological advances by the pharmaceutical industry (e.g., guidance on Part 11, draft guidance on PAT, aseptic processing, and comparability protocols)
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance (e.g., quality systems approach to inspection and the FDA's plan for a quality system for CMC review and other activities)
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas (e.g., emerging model for a risk based approach for inspection site selection and CMC review, and the ICH projects on pharmaceutical development and risk)
- Ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science (e.g., a framework concept to support innovations and scientific

thinking in the draft PAT guidance, associated training and certification of PAT Review and Inspection Team, and formation of the Pharmaceutical Inspectorate)

- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies on review and inspection activities (e.g., draft guidance for technical issues resolution, emerging model for use of Product Specialist during inspections, etc.)

It is intended that these activities will facilitate significant progress toward the "desired state," as articulated below for pharmaceutical development, manufacturing and its associated regulatory policies:

Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes. This initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products. In this regard, the desired future state of pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous "real time" assurance of quality
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product

LINKAGE TO THE ONIDP DOSE CONTENT UNIFORMITY DEBATE

The CDER/FDA recommended specifications for DCU (and DCU through container life) for ONIDP were published in the 1998 draft guidance for industry (8). These recommendations are based on about 10 years of review experience and provide an assurance that products that conform to these standards deliver the labeled dose to patients with acceptably low variability. Based on the clinical need, some exceptions (e.g., wider acceptance criteria) have been accommodated.

The DCU test is designed to demonstrate the uniformity of delivered dose consistent with the product label and provides an overall performance evaluation of a batch; assessing the formulation, the manufacturing process, the valve, and the actuator or other related inhaler components. The recommended DCU is predominately a non-parametric limit test that counts the number of determinations in a sample within and outside certain pre-fixed limits and includes a criterion referred to as a zero tolerance criterion for the test sample (i.e., no test sample is outside 75-125% of the label claim).

International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) has argued that the recommended DCU acceptance criteria is too stringent to encompass all product types, has a high potential for failing good batches, and results in debates during the CMC

review process that delay new drug approvals. They have proposed an alternate method referred to as the Parametric Tolerance Interval Test (PTIT) that is, in-part, based on a publication authored by FDA and USP scientists (9) and has been described further in the preceding article of this volume.

The PTIT is claimed to have several advantages: (a) it is suitable for all ONIDP product types and maintains or improves consumer protection (i.e., provides the same or better guarantee of rejecting a bad batch compared to the current FDA draft guidance) while reducing producer risk (lower risk of rejecting a good batch); (b) it includes a product-specific sample size with the same consumer protection for all sample sizes and a design that utilizes the same test for single and multi-dose products; (c) for multi-dose products it addresses within- and between-container uniformity in one test; and since it is a parametric test, it makes more efficient use of information from each sample and provides more information per test. On average, PTIT increases sample size per test compared to the draft guidance.

The PTIT is also designed to simultaneously control the mean and the standard deviation without the need for a "zero tolerance" limit criterion. It includes constraints on sample mean and standard deviation and claims to provide the specific limiting quality (85% coverage of 75-125% of label claim) as is estimated to be "implied" in the FDA draft guidance. *Limiting Quality* refers to the quality at which 95% of batches will be rejected (5% accepted) and *Coverage* is the proportion of doses in the batch that are within the target interval; batches that have the same coverage of given target interval are considered to be of equal quality (10).

Debate between FDA and IPAC-RS on the acceptability of the proposed PTIT continues today, almost three years after the creation of the initial proposal. Over this period, IPAC-RS representatives have met with FDA staff on several occasions and their proposal discussed with the Advisory Committee for Pharmaceutical Science. As a result of these meetings, significant progress has been made. However, three plus years and remaining unresolved issues suggests a need to improve the efficiency of this process.

There is general agreement that the concept of PTIT can improve the current test when all unresolved issues are addressed. The involved FDA staff and the Advisory Committee agreed that this method should be further developed (11). The current status of PTIT acceptance may be categorized in four parts: (1) consensus between involved FDA staff and IPAC-RS, (2) discussions on statistical procedural issues that need resolution, (3) issues on which consensus has not been achieved, and (4) work that will be necessary to ensure that the consensus outcome of this collaboration is acceptable to FDA and the society before it is adopted. The discussion below identifies significant hurdles and suggests a way forward.

Moving away from the concept of "zero tolerance" (for the test sample) is also an area of general agreement among FDA's involved staff; however, significant (predominantly communication) challenges remain with regard to the perception or concern that this may result in lower quality products reaching the marketplace. It is unfortunate that this terminology has been part of this discussion since it can be misleading. For some, it provides a (false) sense of security that there can be no doses in the batch outside these limits. The current use of this terminology and criteria may have forced the industry into a minimalist testing strategy in order to cope with an untenable situation and can be a significant deterrent to continuous improvement.

The current non-parametric test does not and cannot claim that an acceptable batch will have no doses outside the 75-125% limit. According to IPAC-RS calculations, the draft FDA recommended acceptance criteria (which is a far more stringent criteria compared to the USP criteria) provides 85% coverage of 75-125% of label claim. One interpretation of this calculation is that there is a high probability that about 15% doses in a batch can be outside these limits. This variability can

be inherent in the approved design; therefore, this connects the discussion here, to the potential for *high batch rejection frequencies* in the hypothetical case study discussed above.

The fundamental premise of our pharmaceutical quality system – *that quality must be designed into products* – is a recognition that end product testing alone, with or without zero tolerance, can not eliminate or minimize risk of nonconformance. In the absence of 100% nondestructive testing (e.g., in cases where only a sample can be tested), risks of nonconformance can only be minimized through proper design, development, process understanding, and control, and by ensuring an adequate quality assurance system. To date, these elements have not been a significant part of our discussions in the PTIT consensus development process where the focus has primarily been on the statistical details of the proposed test.

The communication and consensus building challenges associated with this issue should not be underestimated. The October 2003 ACPS meeting provided a good example (11). This revealed diverse opinions among scientists with respect to the issue. For example, on one hand, the view was expressed:

"..I have become convinced after listening to those presentations today that zero tolerance really doesn't mean zero tolerance even though that is what we call it. So, to me, it makes perfect sense that is something that we ought to get rid of. I do like a couple of things about the parametric testing. First of all, it does draw inferences about the batch or the population as opposed to relying on the [sample] batch only. It rewards the analyst for additional sampling by improving the precision of the estimates. So, to me, in my mind, the only thing that is outstanding is this issue about gap and acceptable quality. Again, let me come back to what I said earlier today, I do believe that we have to link that to clinical outcomes..."

While, on the other hand:

"The zero tolerance issue—it has taken me a while to be able to articulate this but I guess the reason I am so averse to discarding it is because of the mind set that it creates, not so much in the consumers but the people who are actually involved in manufacturing. I have a zero tolerance policy in my class for cheating. Does it stop all cheating? Probably not. There are probably a couple of people who get away with something. But I do think it creates the mind set that people who are tempted to do something they shouldn't, wind up not doing it, because of a zero tolerance policy."

These arguments emphasize the need for integrated systems thinking and, therefore, the need for considering future PTIT consensus development activities under the umbrella of the Pharmaceutical Quality Initiative for the 21st Century. This integrated systems approach can facili-

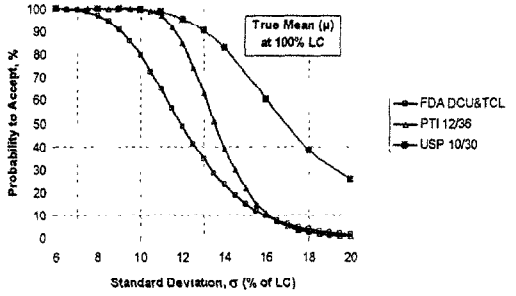

Figure 1. Operating curves for PTIT as proposed by IPAC-RS. Probability of batch acceptance following testing is plotted as a function of the true standard deviation of the delivered doses about the label claim (LC) for the case where the true mean dose = LC. FDA's and USP's presently advocated tests are shown for comparison.

tate clear and complete articulation of concerns and issues and, thereby, provide a means to find efficient and effective solutions for all remaining issues; from perceptions to unresolved major areas of debate (the "Gap"; see below).

Before discussing the issues surrounding the "Gap" it is important to note that there are several statistical procedural aspects of PTIT that need to be resolved, for example, the robustness of the PTIT for non-normal distributions (type I error) remains to be discussed. It is generally expected that these issues can be resolved with minimal debate and those interested in learning more about these issues should review Dr. Adam's presentation at the October 2003 meeting of ACPS (12).

The "Gap" refers to the difference between the operating characteristic (OC) curves (Figure 1 is taken from B. Olsson's presentation at ACPS Meeting, 13 Mar 2003) of the current FDA recommended test in the draft guidance, and that of the proposed IPAC-RS limiting quality of 85% of the doses in the batch within 75-125% of label claim.

A concern raised by this "Gap" is that the proposed PTIT allows "excessively large batch standard deviations" relative to FDA's DCU test over much of the OC range of relevance affecting the actual manufacture of ONIDP. The advocated increase in this allowed standard deviation (the magnitude of the "Gap") is a function of the particular limiting quality, the acceptance probability, and the deviation of the product mean from the label claim. The magnitude of the difference in allowable standard deviations between the two tests, and thus, the choice of limiting quality, is of major concern.

Without a clear understanding of the clinical connection, critical product and process variables, effectiveness of the process control systems, and the potential product/process failure modes, from a CMC review perspective it is difficult to appreciate the notion that the current FDA test may be too restrictive. It is also generally difficult to appreciate IPAC-RS' claim that there is a high likelihood that the quality of the batches rejected may not be very different from the quality of those which are accepted.

In most cases, pharmaceutical development information is not included in the CMC sections of applications received by CDER/FDA (even though this has been held on site for audit during CGMP inspections). Absence of this information, in some ways, may have focused the attention of CMC reviewers and forced a conservative approach to setting specifications, as the only available tool to minimize their concerns on behalf of the US patient. A further dimension which has added problems to the CMC review process has been a less than optimal appreciation of what is accomplished during *process validation* efforts; this for two prominent reasons: a less than optimal interaction has existed between CMC experts (particularly in CDER) and their colleagues conducting CGMP inspections. Also criticisms have appeared (in scientific literature and elsewhere) which imply that the practice of process validation may not have science and engineering focus or may be losing its focus on science and engineering (references 13 and 14 are two examples). Many aspects of the PTIT (for example, verification of normality, deviations from normality, the underlying engineering reason for such deviation, and sample plan based on this understanding, can and probably should be considered part of a validation program and will help to improve its scientific underpinning).

To appreciate just how far apart the two regulatory sub-systems (CMC review and CGMP inspections) are, the following quote from one of the best and most respected CMC Team Leaders in CDER (published in the October 2003 issue of the Gold Sheet: An F-D-C Report) is illustrative:

"Closer cooperation between ORA and the Center review chemists: I can tell you that I have been here for 15 years and it is still not completely clear to me, even after having taken some GMP training recently, what exactly it is that the ORA folks look for.....we don't really understand what the field folks do and I think the field folks are not completely clear on what we do...these current initiatives...are going to bring us closer together..."

Future developments between FDA and the industry must seek to resolve some of these differences in order to better serve the health needs of society and assure the public an uninterrupted supply of quality pharmaceutical products, manufactured and regulated using state-of-the-art techniques.

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