FACILITY AUTOMATION MANAGEMENT ENGINEERING SYSTEMS
33 Hoffman Avenue Lake Hiawatha, NJ 07034-1922

Thursday, 30 October 2003

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 03D-0380

FORMAL COMMENTS ON:

"Draft Guidance for Industry on PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance "

Pursuant to a "request for comment" in ***FEDERAL REGISTER*, Vol. 68, No. 172**, pp 52781 – 52782.

A draft embodying many of these comments was submitted to the Advisory Committee for Pharmaceutical Science (via e-mail: **scharenh@cder.fda.gov**) on 12 October 2003 pursuant to their 3 October 2003 request for public input

The comments being provided are based on an intermediate-level review of the **"Draft Guidance for Industry on PAT —A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance** [http://www.fda.gov/cder/guidance/5815drft.doc – 09/08/03]."

The "reviewable" text begins on page "4;" this review and commentary begins on page "6" at **Line 84**.

This review adds elements that connect various issues in the Draft provided by the Agency to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which this guidance is required to be congruent.

In general, the comments are in the current font, "News Gothic MT."

When a wording change within existing wording is suggested, the comment text is entered in an *italicized News Gothic MT* font.

When text additions are presented, they are placed within quotation marks (" ") in the "News Gothic MT" font.

Explanatory remarks and notes are indented on both margins.

The original text is presented in a "Times New Roman" font and quoted references to CGMP are presented in a "**Lydian**" font.

Should anyone in the Agency who reviews said comments need clarification on a given suggestion, then, they should e-mail reviewer@dr-king.com their questions and, where appropriate, this reviewer will provide additional clarifying remarks.

Respectfully,

This Reviewer

2003D-0380

EMC 2

REVIEW COMMENTS TO: Draft Guidance for Industry on *PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*

1 Page "6"

Lines "84—87" – "Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to ensure quality. ~~This~~ *Unfortunately, this* conventional approach has been *less than* successful in providing quality pharmaceuticals to the public."

"Outside of labeling, most of the recognized post-release drug product failures can be traced to a failure of the manufacturer to fully comply with at least one of the current "inspection (sampling and testing)" CGMP regulations governing those that manufacture, process, or hold a drug product."

The reality is that today's batches typically are not manufactured in full compliance with the clear requirements of the CGMP regulations governing the manufacture of drugs and drug products and are, therefore, not of the quality that said regulations require them to be.

To state otherwise is to knowingly misrepresent that reality and to continue to mislead the public.

2 Page "6"

Lines "87—95" – "However, today significant opportunities exist for improving the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development, process controls, and modern process analytical chemistry tools. Unfortunately, the pharmaceutical industry generally has been hesitant to introduce new technologies and innovative systems into the manufacturing sector for a number of reasons. For example, one reason often cited is *regulatory uncertainty*, which may result from the perception that our existing regulatory system is rigid and unfavorable to the introduction of new technologies. In addition, a number of scientific and technical issues have been raised as possible reasons for this hesitancy."

"In reality, the main reason for their hesitancy is the same as the underlying reason for the industry's reluctance to comply with the current good manufacturing practice (CGMP) regulations governing their conduct, up front and ongoing cost. However, given the recent non-compliance costs to Schering-Plough (a consent decree with a '$ 500,000,000 plus price tag'), hopefully, the industry has finally begun to understand that the overall costs of non-compliance far outweigh the costs of compliance."

Historically, the industry has resisted making changes that increase their input costs even in cases where the overall long-term benefits of the change can be projected to outweigh the costs.

One clear example of this is the industry's reluctance to impose stringent physical characteristic acceptance specifications on the components used in the manufacture of solid dosage forms.

Including a reminder of the future risk (a consent decree with a significant up-front monetary cost) may help the industry to elect to bring their operations into compliance with the CGMP minimums.

3 Page "6"

Lines "96—100" – "Nonetheless, industry's hesitancy to *fully comply with CGMP and to* broadly implement new pharmaceutical manufacturing technologies ~~is~~ *are* undesirable from a public health perspective. The health of our citizens and animals in their care depends on the availability of *unadulterated,* safe, effective, and affordable medicines. Efficient *CGMP-compliant* pharmaceutical manufacturing is a critical part of an effective U.S. health care system."

Unless measures are taken to stop the manufacture of adulterated drugs (as the term is defined in **21 U.S.C. 351(a)(2)(B)**), the implementation of the "new pharmaceutical technologies" will simply lead to the production of more batches of adulterated drug products containing some number of ineffective or potentially unsafe units that, for the patients who receive them, are unsafe and/or ineffective.

In the worst cases, the subpotent, superpotent or otherwise out-of-specification units will lead to adverse outcomes including death for some of those who are unlucky enough to get prescriptions that contain such units.

Since most manufacturers do not perform the requisite statistical quality control inspection required for each batch (21 CFR 211.165(d)), neither the manufacturer nor the Agency is presently able, in such cases, to accurately estimate the percentage of non-conforming units in each batch of each drug released to the public.

This reviewer's suggestion is that the FDA needs to take aggressive action to require compliance in this area and to use the data collected to determine the probable risk for each drug product.

For all approved drug products, the Agency should seek consent decrees as they have done for Schering-Plough that will continue until proven full CGMP compliance is established.

4 Page "6"

Lines "102—107" – "~~In the future~~ *At present and for the near term,* pharmaceuticals ~~will~~ have an increasingly prominent role in health care. Pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment). Regulatory policies must also rise to the challenge."

5 Page "6"

Lines "109—113" – "However In August 2002, recognizing the need to free industry from its ~~hesitant~~ *current* perspective, the Food and Drug Administration (FDA) launched a new initiative entitled Pharmaceutical cGMPs for the 21St Century: A Risk-Based Approach. This initiative has several important goals, which ultimately ~~will~~ *should, if attained,* help improve the American public's access to quality *pharmaceuticals and* health care services.

6 Pages "6—7"

Lines "113—127" – "The goals are intended to ensure that:

- The most up-to-date concepts of risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining product quality
- Manufacturers are encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology
- The Agency's submission review and inspection programs operate in a coordinated and synergistic manner
- Regulations and manufacturing standards are applied consistently by the Agency and the manufacturer, respectively
- Management of the Agency's Risk-Based Approach encourages innovation in the pharmaceutical manufacturing sector
- Agency resources are used effectively and efficiently to address the most significant health risks"

should be revised to read as follows:

"The goals are intended to ensure that:

- The most up-to-date concepts of *statistics-based* risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining ~~product quality~~ *full compliance with all current good manufacturing practice ("CGMP")* ***minimums***

Statistics-Based Risk Management and Quality Systems

Long ago, professional gamblers understood that they were in the risk management business.

They became aware that their actions should be dictated by the potential reward balanced against the probability risk.

Moreover, we owe them because they provided the impetus that led to the development of the principles of probability and statistics that are the foundation of today's development and application of risk-based approaches to process management.

Given that reality, how can the Agency recommend doing less?

Similarly, today's "state of the art" in quality management is "Six Sigma."

Practically, "Six Sigma" translates into producing product lots or batches that have probable defectives rates of less than 3.4 units per million units (0.0034 %) in the lots or batches of products that are produced as discrete units.

In contrast, the requirements of CGMP (21 CFR 211.165(d)) are fundamentally, at best, the "Three Sigma" standards of *statistical quality control.*

Practically, the CGMP minimums roughly translate into lots or batches that have probable (95-% confidence level) "percentage nonconforming" rates of on the order of 1 unit per 1,000 (0.1 %) or higher.

Given that today's maximum lots or batches of units are approaching ten million units in size for tablets, this reviewer supports the Agency's decision to:

- Suggest that the CGMP compliance *minimums* are only the floor,
- Encourage the drug-product manufacturers to do better than CGMP requires and
- Offer suggestions as to how this better level of "quality" can be built into today's drug products by incorporating on-, in- and/or at- line process variable analyzers that provide more rapid conformance assessments.

CGMP Compliance Mandated

Both the Federal Food, Drug, and Cosmetic act as amended (**FDC Act**, **21 U.S.C. 351(a)(2)(B)**) and 21 CFR Part 210 (Sec. 210.1 and 210.2) mandate CGMP compliance.

Guidance, especially guidance such as this, cannot legally recommend any course of action that is contrary to the applicable statute (**FDC Act**) or the applicable CGMP regulations (1988 US Supreme Court decision, **Berkovitz, Plaintiff v. United States** [**486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**]).

Moreover, in 1994, Congress amended the **FDC Act** (adding **21 U.S.C. Parts 335a**, **335b**, and **335c**) to criminalize the subversion of the regulatory process for the firms and individuals who engage in such practices.

Though the statute was specifically aimed those that engaged in the generic drug side of the industry, the penalties now apply to all.

This is the case because all of today's firms are directly and indirectly engaged in the generic side of the pharmaceutical industry.

For example, Sandoz, Swiss-based Novartis' renamed generic division, recently became the largest (in terms of sales dollars) generic manufacturer in the world surpassing the mostly generic Israeli-based firm Teva Pharmaceuticals.

- Manufacturers are encouraged to use the latest *proven* scientific ~~advances~~ *technology (best practical technology [BPT])* in pharmaceutical manufacturing ~~and technology~~

Best Available Technology (BAT) versus Best Practical Technology (BPT)

Many of the scientific advances reported do not turn out to be either *scientifically sound* or practical in the real world.

Properly, the guidance should seek to promote the use of BPT and not BAT.

All too often, the "latest scientific advances" turn out to be either *scientifically* unsound (e.g., super water) or not practical in today's world (e.g., hydrogen-powered fuel cells).

Furthermore, until the "latest scientific advances" are turned into systems that are reliable and can be validated, the pharmaceutical

industry would be ill served by any advocacy that attempts to have such unproven advances incorporated into their operational systems.

- The Agency's submission review and inspection programs operate in a coordinated and synergistic manner

  This reviewer agrees with the Agency here.

- ~~Regulations and manufacturing standards are applied consistently by the Agency and the manufacturer, respectively~~ "The Agency consistently enforces all applicable regulations and the manufacturers consistently meet, or exceed, all of the **CGMP** regulations applicable to their operations."

  The preceding is what the **FDC Act** and CGMP require.
  How can the Agency propose a goal that does or accepts less?

- "Management of the Agency's 'Risk-Based Approach' *in a manner that* encourages *scientifically sound* innovation in the pharmaceutical manufacturing sector"

  This a reviewer does <u>not</u> quite know what is meant by the original statement.

  Though the Agency can be in the risk management "business," they <u>cannot</u> be in the management of the risk business – only the manufacturers can manage the risk.

  Properly, the Agency's role should be to ensure that the all parties understand: **a)** what are the risks, **b)** what are the costs associated with each risk, **c)** what are the probabilities associated with each risk, and **d)** what are the worst-case consequences to the public when, however improbable, the worst-case adverse outcome is observed (e.g., the recent case where batches containing "empty" inhalers were marketed and some, who relied on them, were injured or died because their inhalers lacked the requisite level of the active ingredient or ingredients).

  Based on the preceding, this reviewer suggests modifying the language in the manner shown.

  In this way, the need to use a recognized scientifically sound approach is, as it should be, a prerequisite for whatever approach the industry elects to utilize in their efforts to innovate their manufacturing practices and systems.

- "Agency resources are used effectively and efficiently to *attain and maintain CGMP compliance so that the industry can provided the data needed for the Agency to ensure that the Agency can use scientifically sound risk management to* address the most significant health risks"

  Lacking the statistical data required to: **a)** identify the probability of each risk and **b)** properly assess its significance, how does the Agency propose to determine what are the most significant health risks?

<u>Today's Incoming Acceptance Deficiencies</u>

For incoming materials, the Agency allows firms to do **USP** "Identification" tests on samples that are not batch or lot *representative* orn ot known to be batch or lot *representative* in lieu of the required "**identity**" test on representative samples from each shipment of each lot if full testing is performed (21 CFR 211.84(d)(1)) and "**at least one specific identity test**" when the "accept the supplier's 'Certificate of Analysis" option is selected (21 CFR 211.84(d)(2)).

Given the clear requirement for the determination of "**identity**" and the risks associated with non-identity, how is it that both the Agency and the industry continue to pretend that the "Identification" testing done establishes the identity of a component?

Why is it that the industry resists making certain that each lot of each component has the same identity as the lots used to obtain its submission acceptance (for products covered by a DMF or VMF), approval (drugs in general), or license (certain drugs derived from biological systems)?

Some firms are still allowed to sample "one plus the square root of the number of containers" in the incoming lot or batch even though such sampling plans have long been established to be violative of 21 CFR 211.84(b) and 21 CFR 211.160(b)(1).

In addition, the Agency seemingly ignores the requirement in 21 CFR 211.84(d)(2) for the assessment of the ***purity*** of defined-composition components either by the manufacturer or, if the "'COA' option" is used, on the component manufacturer's 'COA' — Assay is NOT ***purity***.

Finally, the Agency does not seem to require rigorous evidence-based justification of the drug-product manufacturer's acceptance specifications for the physical characteristics of each of the incoming components.

Why does the Agency do this even when it, like the industry, knows or should know that these are crucial to the production of CGMP-compliant batches of the drug product?

Today's In-Process Acceptance Deficiencies

For in-process materials (21 CFR 211.110), the Agency does not enforce the requirement to sample and test each batch or lot for active uniformity at the end of each phase (stage or step) in the manufacture of a drug product that contains an active much less the requirement to test each batch or lot for all factors (such as uniformity of the disintegrants, lubes or release control agents in the formula) that may adversely impact the efficacy of the drug product units.

Though one of the tenets of quality is that the controls implemented should detect problems with a product as early in the process as possible, the industry ignores this tenet.

Instead, the industry seeks to do as little early-stage routine quality evaluation as possible.

Why does the industry do this when the CGMP minimums clearly require more?

Today's Drug Product Acceptance Deficiencies

For the drug product, the Draft continues the Agency's apparent decision to ignore:

- 21 CFR 211.165(d) (which clearly requires statistical quality control be used to accept each lot or batch for release) and
- 21 CFR 211.160(b)(3) (which clearly require batch- or lot-representative samples to be sampled).

Together these regulations clearly require the drug product manufacturer to **inspect** (sample and test) sufficient batch-representative dosage units to satisfy the requirements for statistical quality control. [Note: Minimally, compliance today would require the manufacturer to inspect each batch in accord with the "process variability unknown case" (**see Review** Footnote [2B]) of the applicable recognized consensus standards (**ISO 3951** or its American equivalent, **ANSI Z1.9**). Of course, a manufacturer could elect to sample and test more units and select an appropriately higher confidence level.]

Why is it then that the industry ignores this clear requirement and renders its released batches adulterated (**21 U.S.C. 351(a)(2)(B)**)?

Why is it that the Agency lets the industry ignore compliance?

The simplistic answers to all of the preceding questions are "because of the short-term costs of compliance.

However, is Schering-Plough really happy with the recent probable one-billion-plus dollar costs triggered by the harm caused by one of its willful non-compliances?

Does the industry really want to continue to bear the ever-increasing costs (direct and indirect) of their willful non-compliances?

Based on the reality of the preceding, the Agency needs to somehow get the industry to comply with the law and the legal minimum requirements of the applicable regulations.

When that is done, the firms will have, and the Agency should require them to submit, the body of data needed to understand what the risks are, what their probability of occurrence is, and what the potential costs and impacts of each are.

Then and only then should the Agency consider addressing the most significant risks.

From the point of view of CGMP compliance (**21 U.S.C. 351(a)(2)(B)**), the current probability that a given drug (drug substance or drug product) batch or lot is adulterated is close to "1" in most, if not all, cases.

Until the Agency can get this probability to be below the CGMP expectation "<0.001" for all released lots or batches, or the "Six Sigma" limit of "< 0.00001" for most, the Agency should focus its efforts on CGMP compliance.

Instead of commiserating with the industry with how "hard" it is for them to generate uniform batches, tell them that they must use sound science to develop formulations that are mechanically stable.

Quit tolerating their failure to adequately control the physical properties of the components that they are blending.

If the manufacturers have to, they will find the ways to solve the current mechanical instability problems and meet the goal – what firms must do, they find a cost-effective way to do.

Instead of allowing the firms to get away with essentially no batch- or lot- representative testing of samples of up to three doses in size for the active level in only the final blend, tell the firms they must:

- Sample an appropriate number of multiple-unit-dose-sized, batch- or lot- representative samples in a manner that results in minimally or unbiased samples that are sufficient in size to permit the unbiased subsampling and testing of at least three, unit-dose-size or smaller aliquots for each factor that may adversely affect the drug product batch or lot,
- Test provably batch- or lot- representative unit-dose or smaller subsamples from the samples collected for all variable factors (or their surrogates) that may accept the safety, efficacy, or quality of the drug product
- Develop and use provably scientifically sound, representative-sample-based acceptance specifications for all in-coming components, in-process materials, and drug products.

If all are required to do what CGMP requires, the manufacturers will find a cost-effective way to meet the requirements.

Moreover, the costs of the industry's non-compliances (recalls, consent decrees, and litigation) should, at a minimum, be reduced.

8 Page "7"

Lines "128—134" – "Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles."

This reviewer can only agree with the first part of the sentence, "Pharmaceutical manufacturing continues to evolve."

Based on industry-backed papers and submissions, such as the PQRI "recommendation" on the assessment of blend uniformity, the increased emphasis is on:

1. The deliberate disregarding of CGMP requirements for:
   - Representative samples (the PQRI "recommendation" proposed an obviously non-representative sampling plan called "stratified sampling" that guarantees that the results found for the final blend cannot be compared to the results for the tablet samples). [21 CFR 211.160(b)(2)]
   - The testing of a blend for all variables that may affect the drug products ability to meet its specifications (they only test for active level) [21 CFR 211.110]
   - Testing a sufficient number of batch- or lot- representative dosage units under statistical quality control (the PQRI

'recommendation' proposes testing essentially "any" 10 or 30 units and, implicitly, ignoring the CGMP requirement for "statistical quality control" assessment) [21 CFR 211.165(d)]

2. Fails to even acknowledge the existence of much less use the recognized applicable consensus standard plans suitable for batch assessment of dosage-unit acceptability at the 95-% confidence level (**ISO 3951** or, its American National Standard equivalent, **ANSI Z 1.9**)
3. Uses pseudo science (statistical modeling of hypothetical data) in an attempt to clothe their non-scientific approach to the problem and their scientifically unsound dosage-unit "inspection plans" in "science."

Based on the preceding, it would seem that the evolution is away from the recognized consensus standards of inspection science and the CGMP compliance minimums set forth in 21 CFR Part 211.

"Effective use of *valid population statistics, statistical quality control, and* the most current pharmaceutical science and engineering principles and knowledge - throughout the life cycle of a product – can improve the efficiencies of both the manufacturing and regulatory processes."

Currently, most of the data available only reflects the values found for the samples tested.

Because the samples tested are not, for whatever reason, truly population representative, the results obtained cannot validly be used to determine the probable population distribution of the materials tested or the drug product batches produced.

Both 21 CFR 211.110(b) and 21 CFR 211.165(d) speak to the need to establish (prove) that the population (batch), not just the samples tested, meets appropriate specifications.

Because there were and are no recognized consensus standards for the non-discrete material case, 21 CFR 211.110(b) ("Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications") speaks in a general manner to the issues.

Because there were and are recognized consensus standards for the discrete-units case, 21 CFR 211.165(d) (Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels") spells out exactly what is required.

However, in neither case does the regulation contain language that suggests that the acceptance of any material or drug product can be

based upon a manufacturer's finding that the samples evaluated gave results that were within specification.

Both assert that the requirement is that the results obtained must assure that each drug product batch and the in-process materials used to make each batch conform to specifications.

In most cases, all that the limited results obtained do is establish that the samples tested do or do not meet the specifications set by the manufacturer.

In general, even when all of those results meet the manufacturer's specifications, their limited numbers preclude any confident (confidence level of 95 % or higher) assessment as to whether the untested batch from which the tested samples were taken meets or does not meet its specifications.

"This FDA initiative is designed to do just that by using ~~an~~ *a CGMP-compliant, science-based* integrated systems approach to regulating pharmaceutical product quality."

"The approach is based on *the manufacturer's using the appropriate sound* science and *fundamental* engineering principles for assessing and mitigating risks related to poor product and process quality."

9 Page "7"

Lines "135—149" – "In this regard, the desired future state of pharmaceutical manufacturing may be characterized as follows.

- "Product quality and performance are ensured through the design of effective and efficient *CGMP-compliant* manufacturing processes"
- "Product and process specifications are based on a *CGMP-complaint population-statistics-based* mechanistic understanding of how formulation and process factors affect product performance"
- "Continuous ~~*real-time*~~ *near-real-time* quality assurance"
- "Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge and the current recognized consensus target and CGMP-minimum levels for quality"
- "Risk-based regulatory approaches recognize
  - the *CGMP-requred minimum* level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and
  - the capability of *CGMP-compliant population-based statistical* process control strategies to prevent or mitigate the risk of producing a poor quality product"

10 Page "7"

Lines "156—166" – "IV. PAT FRAMEWORK"

"For the purposes of this draft guidance, PAT is considered to be a *CGMP-compliant* system for designing, analyzing, and controlling manufacturing through timely ~~measurements~~ *evaluations* (i.e., during processing) of critical quality and performance *variables and* attributes of raw and in-process materials, *product* and processes with the goal of ensuring final product quality."

Measurement

Properly, analysis systems that do not directly measure the level of responses in a manner that directly translates into a defined level of the variable being accessed should be classified using either the general term "evaluation" (which covers both these systems and those that do directly measure analyte level) or the specific terms, "classification" or "examination."

Therefore, this reviewer will a) use the general term, "evaluation" when the PAT system could be of either type and the terms "classification" or "examination," depending upon the context, when systems that do not directly measure the analyte and b) correct the Draft accordingly.

It is incorrect to assert that:

a) Systems that can only validly classify a sample as probably belonging, or not belonging, to some class (as defined by some training set) measure the sample or

b) Such systems make measurements when the really use complex sample "signatures" to classify the sample as either a member of the acceptable class or not.

As the Draft says at one point, these analyzers see "complex signatures," they do not see discrete or deconvoluted responses that are proportional to analyte level.

These do not test, they do not make analyte proportional measurements, and they should not be represented to do so.

MATERIAL FACTOR TYPES: Variable and Attribute

Properly, there are two (2) types of properties (characteristics) that describe a material.

These are a) variable factors (i.e., quantifiable factors like the weight percentage of water in a material) and b) attribute factors (i.e., qualitative factors like the material's physical state [solid, semi-solid, liquid, or gas]).

Given this reality, one should restrict the term "attribute" to qualitative factors and use the term "variable" when discussing factors that can be quantified.

Unless the process analyzers directly measure the level of a response that is proportional to the amount of the variable factor, the process analyzer operates as a classifier and the evaluations performed are attribute assessments (i.e., classifiers that either classify the

material being evaluated as "conforming" or "not conforming" without providing any valid assessment of how close the material evaluated is to the expectation target when it is classified as conforming (or how far it is from the expectation envelope limits when it is classified "not conforming)."

Given the preceding, this reviewer suggests changing all uses of the term "attribute" to: a) "characteristic" when it applies to both attribute and variable factors" and b) "variable" or "variable factor" when discussing factors that are amenable to quantitative assessment.

Based on the preceding, this reviewer will appropriately replace the term "attribute" with "characteristic" or "variable" or "variable factor" in this Draft unless the term is being properly used to address a qualitative "attribute factor" (e.g., amorphous powder, crystalline, liquid).

"It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner *using population statistics to define the controls and control specifications required to attain and maintain CGMP compliance.*"

"The goal of PAT is to understand and control the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should be by design.*"

"However, statistical population assessment (21 CFR 211.165(d)) is the only way to ensure that each batch of product is, as the FDC Act requires, CGMP compliant."

11 Page "8"

Lines "182—190" – "An emphasis on building quality into products allows a focus on relevant multi-factorial relationships among material, manufacturing process, and environmental variables and their effects on quality."

"*Provided valid, number-sufficient, population-representative data sets are collected for all factors that may adversely affect the process and the product, and the appropriate statistics-based modeling is used to establish the relationships,* these relationships provide a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, training)."

"*When the effects of scale are properly addressed and sufficient population representative data is collected at each stage,* the data and information to help understand these relationships ~~are~~ may be obtained through preformulation programs, development and scale-up studies, and from manufacturing data collected over the life cycle of a product."

12 Page "8"

Lines "192—206" – "A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined *CGMP-compliant or better level* of quality at the end of the manufacturing process."

"Such procedures would be consistent with *CGMP and* the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency."

"Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line ~~measurements~~ *evaluations* and controls (could increase efficiency and perhaps safety but not likely to improve quality, based on automation of other analyses and controls in the clinical laboratory)
- Preventing rejects, scrap, and re-processing (an obvious quality gain)
- Considering the possibility of *near* real-time release (real-time release would "improve" efficiency but would also be non-CGMP-compliant; near real-time release could improve efficiency while maintaining CGMP-compliance)
- Increasing automation to improve operator safety and reduce human errors (safety and possible quality gain but human QCU sign-offs would still be needed and system would have to be fully compliant with both CGMP and 21 CFR 11)
- Facilitating continuous processing to improve efficiency and manage variability
  - Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities
  - Improving energy and material use and increasing capacity"

13 Page "9"

Lines "215—230" – "Pharmaceutical manufacturing processes often consist of a series of unit operations, each intended to modulate certain properties of the materials being processed. To ensure acceptable and reproducible modulation, consideration must be given to the quality ~~attributes~~ *characteristics* of incoming materials and their processability for each unit operation. During the last 3 decades, significant progress has been made in developing analytical methods for chemical ~~attributes~~ *characteristics* (e.g., identity and purity)."

Except for the replacement of the word "attributes" with "characteristics," this reviewer agrees with the Draft.

"However, *manufacturers have not been equally diligent in characterizing and controlling* certain physical and mechanical ~~attributes~~ *variables factors* (e.g., particle shape, size distribution, inter- and intra-particulate bonding) *that are known to affect the performance* of pharmaceutical ingredients."

"*The manufacturers have chosen to claim that such: a)* are relatively difficult to characterize *and b) out of the manufacturer's control ('must take what supplier supplies').* ~~and~~

In this reviewer's experience with products as complex as multiple-vitamin/multiple-mineral vitamin products, these claims are based on the unwillingness of the manufacturer to: **a)** develop adequate controls, **b)** impose (by contract that pays for the extra costs borne by the

supplier) adequate physical-property specifications, **c)** sample lot-representative samples of sufficient size to reduce sampling error to insignificance, and **d)** do the appropriate testing.

The lack is not the science or the overblown difficulties of sampling; it is the lack of will on the part of the drug-product manufacturer — doing what is required costs something.

Why increase raw material costs by any amount even if it is only $US 0.03 a kilo when you can get away with claiming that physical properties can't be properly controlled or the suppliers won't supply the grade needed, or do, or pay for, the requisite testing when you can instead get the FDA to buy into the portrayed "sampling" and "purchasing" difficulties?

"*Thus, the* adverse effects due to *a lack of adequate controls on the* inherent quality variability *in the components* are often not recognized until after manufacture."

"*The manufacturers claim that* establishing effective standards or specifications for physical ~~attributes~~ *characteristics* of raw (e.g., *active ingredients and* excipients) and in-process materials poses a significant challenge because of the ***a)*** complexities of such ~~attributes~~ *variables* (e.g., particle shape and shape variations within a sample) and ~~because of~~ ***b)*** difficulties related to collecting representative powder samples for testing."

"It is well known that the typical powder sampling procedures used by the pharmaceutical manufacturers can be prone to sampling errors."

14 Pages "9

Lines "232—245" – "Formulation design strategies exist that provide robust processes that are not adversely affected by ~~minor~~ differences *allowed by the manufacturer* in *the* physical ~~attributes~~ *characteristics* of raw materials."

"These strategies fall into two well-defined categories,

1. Wet granulation (using aqueous, nonaqueous or mixed aqueous/non-aqueous solvents), and
2. Dry granulation (using one or more compaction, milling, and screening steps to appropriately bind otherwise 'incompatible' [in size, density, and/or binding affinity] components together)."

"*Because these strategies cost time and money, the industry has tried to portray* ~~Because~~ these strategies ~~are~~ as not generalized and ~~are often~~ based on the experience of a particular formulator."

"However, the published 'state of the science' vis-à-vis formulation and process development seems to be at odds with the preceding positions."

"*In any case,* the quality of these formulations can only be evaluated by ~~testing~~ *appropriately evaluating* samples of *the components,* in-process materials and end products."

"Currently, these tests are *usually* performed off line after preparing collected samples for analysis."

"Different tests, each for a particular quality ~~attribute~~ *variable factor* (e.g., content uniformity, moisture content, dissolution rate), are needed ~~because~~ *when, for materials defined by multiple variables,* such tests only address one ~~attribute~~ *variable factor (e.g., level* of the active ingredient*)* following sample preparation (e.g., chemical separation to isolate it from other components)."

"During sample preparation, other valuable information pertaining to the formulation matrix is often lost."

"Several new technologies are now available that can acquire information on multiple ~~attributes~~ *variable factors* with minimal or no sample preparation."

"These technologies provide an opportunity to assess multiple ~~attributes~~ *variable factors,* often nondestructively."

15 Page "9"

Lines "247—252" – " "Currently ~~most~~ *many* pharmaceutical processes are based on time defined end points (e.g., blend for 10 minutes).

"However, in some cases, *because of the lack of adequate material controls and weaknesses in the development of the process,* these time-defined end points do not ~~completely~~ *properly* take into consideration physical differences in *the* raw materials *used in a given process* (~~e.g.~~ *i.e., active ingredients and* excipients)."

"Processing difficulties can arise that result in failure of the product to meet specifications, even ~~if~~ *when* ~~certain~~ *all* raw materials conform to *their* established specifications."

"This is the case because the manufacturer, for whatever reason, fails to have adequate controls on the raw materials and the processing conditions."

16 Page "10"

Lines "254—270" – "Appropriate use of new on- or in-line process analyzers (e.g., ~~vibrational~~ vibration-spectroscopy-based sensors) that provide information related to both physical (e.g., particle size, morphic form, moisture content) and chemical ~~attributes~~ *characteristics* can, *in some cases,* not only address the limitation of *time*-defined end points discussed above, *but also* these tools can improve *the* efficiency of ~~all~~ *some* processes."

The principal difficulty with all sensors is the limitations on penetration depth imposed by being limited to energy levels that do <u>not</u> alter the material being evaluated while the evaluation is being made.

For non-transparent solids, the case that this guidance focuses on, that penetration depth is limited to a few millimeters at best.

Unfortunately, the blender-surface boundary layers in most blending operations are, in most cases, as deep or deeper than the sensors' penetration depth.

Further, except when sophisticated variable-pulse techniques are used with a suitable reference channel to correct for ambient environmental effects, such analyzers only provide "fuzzy" (less than

reproducible) average property assessments of the variables they are "profiling" and classifying.

Moreover, to use such on- or in-line process analyzers, the training sets (acceptable, unacceptable, boundary) (used to enable them to properly assess (classify) the materials for which they are being used) must encompass all possible conditional sets that are acceptable as well as sets that clearly establish what is unacceptable.

In addition, the complexity of the signals produced and the overlap among the signals from various mixtures of multiple components combine to make the size of the training sets required orders of magnitude larger than when such analyzers are used to assess the variable properties of a single discrete raw material.

While there are scientifically sound and appropriate cases where such analyzers have been used to accurately classify incoming discrete components and the assay level of a single active in small single-layer tablets, scientifically sound and appropriate uses of such classification analyzers for assessing: a) even three-component mixtures where the individual components are themselves complex variable-property solids or b) all critical factors (USP specified factors that must be assessed post-release, such as, active level, active availability [Dissolution or Drug Release], moisture level, key impurity level, residual solvents level, etc.) for a single-layer single-active uncoated tablet have not, to this reviewer's knowledge, been demonstrated even in such simple cases

"To be useful in cases *where the use of such is scientifically sound* (21 CFR 211.160), the ~~measurements~~ *evaluations* collected from these types of sensors need not be absolute values of the ~~attribute~~ variable factors of interest."

"However, they must be reproducible, precise, appropriately accurate, and material-representative (location, container, or batch) assessments of the variable factors of interest."

"The ability to *accurately* ~~measure~~ *evaluate lot-shipment-representative* (21 CFR 211.84(b)) relative differences in powder materials before (e.g., within a lot, lot-to-lot, different suppliers) and during processing along with current tests, ~~if~~ *where* necessary[2A], for qualifying incoming raw materials ~~will~~ *can* provide useful information for process control."

"[2A] To meet the requirements of CGMP, at least one "**identity test**" (21 CFR 211.84(d)(1)) must be performed when full testing is performed on lot-representative samples (21 CFR 211.84(b)) and, if a vendor's 'report of analysis is being used to accept components, the regulations require the manufacturer to perform "**at least one specific identity test**" (21 CFR 211.84(b)(2)) on lot representative samples (21 CFR 211.84(b)). When the on-, in-, or at- line analyzer used does not truly measure identity but instead classifies a material as "acceptable" or "unacceptable," as, for example, most Near-Infra-Red (NIR) analyzers do, the evaluation, while it may be useful to providing assurance that each container of a component is "comparable" to some training set of acceptable materials" is **not** a test. In such cases, the testing requirements of the CGMP must be met or the product produced will be adulterated. For such, the manufacturers should

perform the requisite tests if they wish to even offer their drug products for sale in the United States. This is the case because it is a crime to offer such adulterated drug products for sale in the United States."

"A *pre-established* degree of flexibility in process conditions (e.g., time) ~~should~~ can be applied to manage differences in the physical ~~attributes~~ *characteristics* of the materials being processed *provided the flexibility is supported by scientifically sound and appropriate process development studies.*"

"~~Such~~ *Provided sufficient material-representative evaluations are made, such* an approach can be established and justified when differences in physical ~~attribute~~ *characteristics* and process ~~end points~~ *end-point evaluations* are used to control (e.g., feed-forward and/or feed-back) ~~the~~ *a given* process *step.*"

"~~An~~ *In such case, as it often is currently for moisture level in drying operations, an* end point would be determined based on the desired ~~attributes~~ *variable factor characteristics* of the materials necessary for the next unit operation (e.g., acceptable blend uniformity, granule size, moisture control)."

17 Page "10"

Lines "274—288" – "There are many current and new tools available that ***may*** enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance."

"These tools, when used within ~~a~~ *an adequately characterized* system, can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge."

"In the PAT framework, these tools can be categorized ~~according to the following~~ *as follows*:

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools"

"An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance."

18 Page "10"

Lines "292—297" – "From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many different development strategies that can be used to identify optimal formulation and process conditions for these systems."

"However, the scientifically sound and appropriate strategies fall into two (2) broad categories, a) designed condition-spanning experimentation (most typically using factorial or sub-factorial experimental designs) or b) direct-search condition spanning experimentation (a category that is little used in the pharmaceutical industry)."

"In both scientifically sound strategies, once the region or regions where acceptable uniformity and performance are identified, mapping algorithms augmented, where needed, by confirmatory experiments are used to define the mechanistic systems from which the needed control levels and specifications can be established and justified."

"The success of such developmental strategies hinges on the adequacy of the controls on the incoming components, environmental conditions, the equipment used, and the individual process steps."

"These are crucial to the successful development of the process."

"~~The~~ *Provided the developmental strategy used is scientifically sound and appropriate, the* knowledge acquired in these development programs ~~is~~ *can validly be used as* the foundation for product and process design."

19 Page "11"

Lines "299—314" – "This knowledge base can be helpful to support and justify flexible regulatory paths for innovations in manufacturing and postapproval changes. Opportunities need to be identified to improve the usefulness of available relevant product and process knowledge during regulatory decision making — without affecting a manufacturer's development program."

"A knowledge base can be of most benefit when it consists of ~~both~~ a scientific understanding of the relevant multi-factorial relationships (e.g., ~~between~~ *among* the properties of the *components,* formulation, process, and *product* quality ~~attributes~~ *factors*) as well as a means to evaluate the applicability of this knowledge in different scenarios (i.e., generalization)."

"To achieve this benefit, some manufacturers use multivariate mathematical approaches, such as statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools, *in conjunction* with knowledge management systems"

"~~The~~ *Provided the variability in the components used in the system are adequately defined and controlled,* the applicability and reliability of knowledge in the form of mathematical relationships and models can be assessed by statistical evaluation of model predictions *vis-à-vis the actual observed product outcomes.*"

20 Page "11"

Lines "316—323" – "Methodological experiments (e.g., factorial design experiments) based on statistical principles of orthogonality, reference distribution, and randomization provide effective means for identifying and studying the effect and interaction of *component,* product and process variables."

"Traditional one-factor-at-a-time experiments do not effectively address interactions between product and process variables."

"~~Interactions essentially are the inability of the one factor to produce the same effect on the response at different levels of another factor~~. "In multifactor experiments, interactions

are those parts of the effects observed (results) that cannot be accounted for solely by the levels of the factors studied in the experiments."

"Unfortunately, pharmaceutical systems are complicated by the variability in the components assigned as factors in such studies."

"Thus, the apparent interactions observed may be partially connected to the usually "not well characterized" variability in the specific component aliquots used in each experiment even though most of the standard statistical programs used do not even consider, much less adequately address, this reality."

"To properly address component variability, iterative replication of a significant number of the designed experiments (using various combinations of components from different [unrelated] lots) is required to separate component variability from component and processing interaction effects."

"Regrettably, the experimental development studies conducted by most firms seem to ignore, or, at best, minimally address, the preceding reality."

21 Page "11"

Lines "325—336" – "Experiments conducted during product and process development can serve as the building blocks ~~of knowledge~~ *for the understanding of the process* that ~~grow~~ *can evolve* to accommodate ~~a~~ higher degree of complexity *as the factor and results data sets grow* throughout the life-cycle of a product."

"Information from such structured experiments *can be used to* support *the* development of a knowledge system for a particular product and its processes, *provided the experiments are scientifically sound and the permitted variability in the components used in the process is properly addressed.*"

"This information, along with information from other *similarly sound* development projects, can then become part of ~~an~~ *a scientifically sound and effective* overall institutional knowledge base."

"As this institutional knowledge base grows in coverage (range of *components, processes,* variables and scenarios) and data density, it can be mined to determine useful patterns for future development projects."

"These experimental databases can also support the development of process simulation models, which can contribute to continuous learning and help to reduce overall development time."

22 Page "11"

Lines "338—343" – "Today's information technology infrastructure makes the development and maintenance of this knowledge base practical."

"When used appropriately, the tools described above can help identify and evaluate *component,* product and process variables that may be critical to product quality and performance."

"The tools may also help in identifying potential failure modes and mechanisms and in quantify their effects on *both process capability and* product quality."

23 Page "12"

Lines "292—297" – "The types of knowledge that will be useful when introducing new manufacturing and quality assurance technologies would be expected to answer the following types of questions (examples):

- What are the mechanisms of degradation, drug release, and absorption?
- What are the effects of product components on quality?
- What sources of variability are critical?
- Where in the process should the controls be instituted?"

should be changed to:

"The types of knowledge that will be useful when introducing new manufacturing and quality assurance technologies would be expected to answer the following types of questions (examples):

- What are the mechanisms of degradation, drug release, and absorption?
- What are the components and processing steps that should be used to manufacture the initial, clinical, and projected approved dosage forms?
- What sources of variability are critical?
- For the clinical and projected approved dosage form, what are the key physical and chemical properties of the components selected, the controls needed for the key components, and the control ranges needed for each key property of each component?
- What are the effects of product components' ***levels*** *and processing conditions* on *product* quality *and product acceptability*?
- Where in the process should the controls be instituted?"

24 Page "12"

Lines "355—366" – "b. Process Analyzers ~~or~~ and Process Analytical Chemistry Tools"

"~~Process~~ *The use of process analytical technology (PAT)* ~~chemistry as a discipline~~ has grown significantly during the past several decades."

"The increase in the usage of PAT has been driven by ~~due to~~ an increasing appreciation for the value of collecting process data during production and the advances in instrumentation, sensors, and data processing power.

"Chemical industry drivers, ~~of~~ *including the need to a) address and minimize the effects of feed variability, b) increase* productivity, *c) improve* quality, and *d) minimize adverse* environmental impacts, have supported major advancements in this area."

"Available tools have evolved from those that take simple process measurements, such as pH, temperature, and pressure, to those that measure chemical composition *(e.g., GC-TCD/EC/MS, LC-UV/RI/MS, ICP-Light Adsorption/MS, and NMR)* and physical

~~attributes~~ *variable factors (e.g., color, density, viscosity, particle size distribution, flow).*"

"Some modern process analysis tools provide nondestructive ~~measurements~~ *evaluations* that contain information related to both *the* physical and chemical ~~attributes~~ variable factors of the materials being processed."

25 Page "12"

Lines "366—378" – "These ~~measurements~~ *evaluations* can be:

- off-line, in a laboratory, *where the samples are removed from the processing area, transported to the lab, and evaluated*
- at-line, in the production area, where the samples *are evaluated* during production *in an area* close to the manufacturing process
- on-line, where the ~~measurement~~ *evaluation* system is connected to the process via ~~a diverted~~ sample stream diverter; periodically, a sample from the process is diverted and evaluated; and, in favorable cases; the sample ~~may be~~ *is* returned to the process ~~stream~~ after ~~measurement~~ *evaluation*
- *invasive* in-line, where *the* process ~~stream may be~~ *is* disturbed (e.g., probe insertion), and ~~measurement~~ *evaluation* is done in real time
- noninvasive *in-line*, ~~when~~ *where* the sensor is not in contact with the material (e.g., Raman spectroscopy through a window *in the process equipment*) ~~in the processor~~, *and* the process stream is not disturbed"

Properly, all evaluations, except in-line evaluations, are, by virtue of the sampling mechanisms used invasive to some degree. In-line evaluations are either invasive or noninvasive depending upon the manner in which they evaluate the process. Thus, the term "noninvasive should be used as an adjective to differentiate between the two (2) types of "in-line" evaluations and, not as the draft does, defined without respect to the evaluation point.

26 Page "12"

Lines "379—386" – "Many of these recent innovations make real-time control and quality assurance during manufacturing feasible."

"However, multivariate mathematical approaches are often necessary to extract this information from complex signatures and to correlate these results to a primary method of analysis."

"The most critical problem in this area is ensuring that the correlations found are truly correlations between the changes in the samples and the test results observed."

"For example, when using Near-IR to assess component purity, the Near-IR adsorption bands chosen must be directly relatable to the structural features of the compound."

"If this is not the case, future batches, as has been found in more than one instance, may be improperly classified as failing when they do not or, worse, passing when they fail."

"The next most critical problem in this area is having analyzer training sets that include representative examples of both passing/conforming materials and failing/non-conforming materials that appropriately span the entire possible ranges."

"The third critical problem is the evaluation of sufficient population representative samples to insure that the overall classification arrived at by the trained validated evaluation systems is valid. [**Note:** Typically, in dynamic systems equipped with short-range sensors in much wider vessels, some significant multiple of the number of evaluations required in static systems will need to evaluated.]"

"In the discrete entity case, the numbers in the recognized attribute inspection (sampling and evaluation) plans (e.g. ***ANSI/ASQ Z 1.4***) for the "process variability unknown case"[2B] can be used as the basis number with the multiplier being determined by the level of residual variability in the system."

"[2B] The restriction to the "process variability unknown case" arises because the variabilities in the key physical property factors of the components used in the process are: **a)** not, for whatever reason, rigorously controlled and/or **b)** the allowed variabilities in said properties, and not just the levels of the components and their interactions, can be significant factors in determining the outcomes observed."

"~~A~~ *When the validity of the correlations, the adequacy of the training sets have been established, and sufficient population representative evaluations have been made, a* comprehensive statistical ~~and risk~~ analysis of the process is generally necessary to assess ***a)*** the reliability of the predictive mathematical ~~relationship~~ *relationships established and* ***b)*** *the risks associated with the failure of the each of the correlations thus established* prior to implementation."

"Based on the estimated risk *and the level of confidence in the correlations generated,* a correlation function may need further support or justification."

27 Pages "12—13"

Lines "386—394" – "This *support or justification* may be in the form of mechanistic explanation of *the* causal links between *the inputs (components and/or prior step materials),* ~~process~~ *the processing steps,* ~~material measurement~~ *and the evaluated outputs as they impact and are impacted by the* target quality specifications ***minimums*** *required by CGMP."*

"For certain applications, sensor-based ~~measurements~~ *evaluations* can provide a useful process signature that may be related to the underlying *acceptability of the* process steps or transformations."

"Based on the level of process understanding, these signatures may also be useful for process monitoring, control, and end point determination when these patterns or signatures *can be*

established (proven) to reliably relate to product *acceptability* and process ~~quality~~ *capability.*"

28 Page "13"

Lines "396—399" – " "Design, ~~and~~ construction, *and qualification* of the process equipment, the analyzer, and their interface are critical to ensuring that collected data are relevant and representative of process and product ~~attributes~~ *variable factors.* Robust design, reliability, and ease of operation are important considerations."

29 Page "13"

Lines "401—406" – "A review of current practice standards (e.g., ASTM) for process analyzers in other industries can provide useful information and facilitate discussions with the Agency. A few examples of such standards are listed in the bibliography section."

"We recommend that manufacturers developing a PAT process consider a *CGMP-compliant,* scientific, ~~risk-based~~ *risk-adverse* approach relevant to the intended use of an analyzer for a specific process."

30 Page "13"

Lines "410—423" – "Design and optimization of drug formulations and manufacturing processes within the PAT framework can include the following steps (the sequence of steps can vary):

- Identify and measure critical *component,*m aterial and process ~~attributes~~ variable factors ~~relating to product quality~~ **"that may be responsible for causing variability in the characteristics of in-process material and the drug product"** *(21 CFR 211.110(a))*
- Design a process ~~measurement~~ *evaluation* system to allow real time or near-real time (e.g., on-, in-, or at-line) monitoring of all critical ~~attributes~~ *variables that developmental studies establish can affect the acceptability of the product produced in a given step*
- Design process controls that ~~provide~~ *permit pre-established* adjustments to ensure *adequate* control of all critical ~~attributes~~ *variable factors and process outcomes*
- Develop *valid* mathematical *correlation* relationships betweenp roduct ~~quality attributes~~ *requirements* and ~~measurements~~ *evaluations* of critical *component,* material and process ~~attributes~~ *variables.*"

31 Pages "13—14"

Lines "366—378" – "Therefore, it is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical ~~quality attributes~~ *component, material, and product variables.*"

"Process monitoring and control strategies are intended to monitor *and validate (21 CFR 211.110)* the state of a process and, *within pre-established limits,* actively manipulate it to maintain ~~a desired state~~ *the required outcomes.*"

"Strategies should ~~accommodate the attributes of~~ *explicitly address: a) the critical variable factors for the* input *components and* materials, *b)* the ability and reliability of process analyzers to ~~measure~~ *evaluate the* critical ~~attributes~~ *variable factors*, and *c)* the achievement of pre-established process endpoints to ensure consistent ~~quality of~~ *batch conformance to specifications for each batch of* the output materials and the final product."

32 Page "14"

Lines "434—442" – "Within the PAT framework, a process endpoint need not be a fixed time, but can, *within pre-established limits,* be *defined by* the achievement of ~~the desired~~ *a predefined* material ~~attribute~~ *specification (e.g., a LOD [loss on drying] of less than 1 %).*"

"This, however, does not mean that process time is not considered. A range of acceptable process times (process window), ~~is~~ likely to be achieved during the manufacturing phase ~~and~~ should be evaluated, and ~~considerations~~ provisions for addressing significant deviations from *the predetermined* acceptable process times should be developed."

"Process end points intended for use in *"**near**-real-time" release* should be considered more ~~critical~~ *critically* than those that are only used for in-process control."

CGMP does not permit automatic "real time" release of materials from step to step (phase to phase or stage to stage) or release for distribution. Therefore, provision must be made for the QCU to review the data and either release, reject, or require additional assessment of the batch of material or product to the next controlled step, stage or phase covered by CGMP.

Thus, the maximum that the Agency can legally, or should, recommend is "*near-real-time*" release.

33 Page "14"

Lines "444—454" – "Where PAT spans the entire manufacturing process, the fraction of *components,* in-process materials and final product evaluated during production could be substantially greater than ~~what is currently achieved using~~ *the often non-CGMP-compliant inspection practices used by many firms that minimize* laboratory testing *by ignoring the explicit requirements set forth in 21 CFR Part 211 for the acceptance inspection (sampling and testing) of: a) incoming components (21 CFR 211.84(b) and (d) and 21 CFR 211.160(b)(1)), b) in-process materials (21 CFR 211.110(b) and 21 CFR 211.160(b)(2)) and c) the drug product (21 CFR 211.160(b)(3) and 21 CFR 211.165(d)) inspection.*"

"This is the case because valid static PAT typically requires at least an order of magnitude more batch-representative evaluations than testing, and dynamic PAT requires several time that number, before a valid assessment of the acceptability of an in-process batch can be reached."

"Moreover, the drug product CGMP, by explicitly requiring the use of statistical quality control (SQC, 21 CFR 211.165(d)), makes the use of PAT a non-permissible choice for the acceptance of the drug-product batch for release."

"In addition, the in-process findings by a PAT classifying analyzer, even if valid, preclude the use of that data to reduce the number of samples required for valid SQC assessments."

"This is the case because such findings provide no measures of the variability of the in-process batch at each stage."

> In contrast to the preceding, were the manufacturer to properly inspect (sample and test) a batch-representative set of samples for its critical variable properties at each stage, that manufacturer could, if the preceding test shows that the outputs of the previous steps are sufficiently uniform with respect to all of their critical variable factors, justify the use of the reduced inspection plans available in the recognized consensus standards for the testing of units for their variable factors.
>
> In the most favorable cases, this would translate into a reduction from the need to test sets of 200 batch-representative units to the testing of 42 batch-representative units (a "5"-fold reduction) for each critical (USP specified) variable factor with little or no increased risk in releasing a batch that, post release, will be found to be unacceptable.
>
> In such cases, adaptive hierarchical (staged) inspection plans can be used to regulate the level of testing required – increasing it when the uniformity data properly indicates a higher level of testing is needed and decreasing it when the uniformity data indicate that a lower level of testing is appropriate.

"~~Thus, an~~ *However, such classifying analyzers do provide the manufacturer with another* opportunity to ~~use more rigorous~~ *apply* statistical principles ~~for a quality~~ *to its in-process acceptance/rejection* decision *practices* ~~is provided~~."

"~~Multivariate~~ *Thus, multivariate* Statistical Process Control ~~can be~~ *is* feasible and, *when properly applied, can be a* valuable *adjunct* to realizing the full benefit of ~~real-time measurements~~ *real-time and near-real-time evaluations*."

"Similarly, rigorous statistical principles should be used for defining the acceptance criteria for end product ~~attributes~~ *variable factors* (e.g., content uniformity)."

"*These should* ~~that~~ take into consideration *the testing requirements of the CGMP regulations and the* differences in the nature of the ~~test~~ *evaluation* (e.g., ~~continuous monitoring~~ *measurement, or examination and/or classification*), and *the number of samples and the intrinsic* sample ~~size~~ *volume or mass* between an ~~on-line test~~ *on- in- or at- line evaluation* and a current laboratory test."

> The Draft improperly uses the term "test" when the on- in- or at- line evaluation is a classification and not a measurement.

Most of the PAT analyzers currently being used in the evaluation of solids are classifiers; they do not perform tests (which require measurements) because they do not measure.

This reviewer takes a dim view of those who claim to be knowledgeable in the PAT area but seem to knowingly misuse such terms in an apparent attempt to obscure the reality that such PAT classifiers are not and cannot validly be classified as testers that do test and measure.

When the on-. in-, or at- line PAT system is a valid test system, then its results can be used in the setting of CGMP-complaint (*scientifically sound* and *appropriate*) batch release specifications in the same manner that the results from the CGMP-compliant test sets mandated in the drug product regulations can, *when the data satisfies the requirements established therein*, be used to set such.

When the on-, in-, or at- line PAT system is a system that can only classify samples into categories, the results from such systems cannot be used to set CGMP-compliant test specifications.

The Draft needs to explicitly address this reality and not, as it seems to do, obscure or misrepresent this and the preceding realities.

34 Page "14"

Lines "456—465" – "~~Real-time or near-real-time~~ *Real-time or near-real-time* ~~measurement~~ *evaluation* tools typically generate large volumes of data."

"~~Certain data are likely to be relevant for routine quality assurance and regulatory decisions~~."

"In a PAT environment, batch records should include *the same CGMP-complaint* scientific and procedural information ~~indicative of high~~ *that establishes the acceptability of the process and the* product ~~and process quality~~ *as that required currently.*"

"However, the volume of data should be an order of magnitude or more larger than that required to show CGMP compliance in the current environment."

"For example, *when the on-, in- or at- line analyzers truly make measurements, the* batch records ~~could~~ *should* include a series of charts ~~depicting acceptance ranges, confidence intervals, and distribution plots (inter- and intrabatch) showing~~ displaying the measurement results *obtained in terms of their acceptance ranges, confidence interval estimates, intrabatch distribution plots, control charts, updated global process envelope and the like.*"

"When the on-, in- or at- line analyzers classify the samples, the batch records should include the appropriate attribute counterparts to the variable charts."

"Ease of secure access to these data is important for real time manufacturing control and quality assurance."

"~~Installed~~ *In such cases, the firm's installed* information technology systems should *be fully compliant with all of the requirements of 21 CFR Part 11 and* accommodate such functions.

35 Page "14"

Lines "467—473" – "Technologies that ~~incorporate~~ *facilitate the provision of* greater product and process understanding can provideah igh assuranceo f ~~quality on~~ *CGMP compliance for* every batch and provide alternative, effective mechanisms to ~~achieve validation~~ *establish the validity of the process.*"

"In a PAT framework, process ~~validation~~ *validity* can be enhanced and ~~possibly consist of continuous quality~~ *CGMP-compliance* assurance *can be increased* when ~~where a~~ *each* process *step* is continually monitored, *its conformance to targets is concomitantly* evaluated, and, *within pre-established limits, parameters and time frames* adjusted using validated in-process ~~measurements,~~ *evaluations* (tests *and examinations*), controls, and process endpoints."

36 Pages "14—15"

Lines "474—478" – "Installation of process analyzers on existing process equipment in production should be done after risk-analysis to ensure this installation does not adversely affect the process or product quality (i.e. qualified equipment, ~~and~~ validated process, *and CGMP-compliant product*)."

"Based on this assessment, it should be decided if *any part of* the existing process should be ~~revalidated~~ *additionally qualified* or not.

37 Page "15"

Lines "480—485" – "~~Risk-based~~ *Risk-assessment-based* approaches are suggested for the validation of PAT software systems."

"The recommendations provided by other FDA guidances such as General Principles of Software Validation[3] should be considered.

"Other useful information can be obtained from consensus standards, such as *ANSI, ASQC (now ASQ),* ASTM, *BR, IEC, ISA, ISO,* and Good Automated Manufacturing Practices (GAMP) listed in the bibliography section."

"[3] See guidance for industry and FDA staff, *General Principles of Software Validation.*"

38 Page "15"

Lines "489—495" – "Continuous learning through *the continual analysis of the batch-representative* data ~~collection and analysis~~ *collected* over the life cycle of a product is important."

"~~Data~~ *The appropriate analysis of the batch-representative data collected* can contribute to justifying proposals for postapproval changes including *the* introduction of new technologies."

"Approaches and information technology systems that support knowledge acquisition from such ~~databases~~ *data collections* are valuable for the manufacturers and can also facilitate *the sharing of* scientific ~~communication~~ *information* with the Agency."

39 Page "15"

Lines "499—506" – "A process is generally considered well understood when (1) all critical sources of variability are identified, *properly controlled,* and explained; (2) variability is managed by the process;a nd, (3) productq uality ~~attributes~~ *variability* can be accurately and reliably predicted ~~over the ranges of~~ *to be within the* acceptance criteria established for materials used, process parameters, ~~and~~ manufacturing environmen~~tal~~ and other conditions."

"The ability to accurately predict ~~reflects~~ requires a high degree of process *control and* understanding."

"Although retrospective process capability data ~~are~~ *can be* indicative of a state of control (*provided sufficient batch-representative data is available for each batch or lot produced),* these alone may be insufficient to gauge or communicate process understanding."

40 Page "15"

Lines "508—519" – "The emphasis on process understanding provides a range of options for qualifying and justifying new technologies such as modern on-line process analyzers intended to ~~measure~~ *evaluate* and, *when active feedback and feed-forward mechanisms are included,* control physical and/or chemical ~~attributes~~ *variable factors* of *the* materials to achieve ~~real time release~~ near-real-time acceptability for release.

For example, if process knowledge is not shared or communicated when proposing a new process analyzer, the test-to-test comparison between an on-line process analyzer (e.g., ~~NIR spectroscopy for content uniformity~~ *on-line automated UV/visible active uniformity assessment system)* and a conventional test method (e.g., a wet chemical test) on collected samples may be the only available option.

"Similarly, when proposing a new process analyzer, the *evaluation-to-test* comparison between an on-line classifying analyzer (e.g., NIR spectroscopy for content uniformity confirmation) and a conventional test method (e.g., a wet UV/visible content uniformity test) not only requires an extensive comparison between collected samples but also requires the preparation of comparable 'known definitely passing,' and 'known definitely failing' training sets for the initial signature identification and training of the analyzer as well as 'known marginally passing' and 'known marginally failing' samples sets for the confirmatory training of the analysis system."

"In addition, unless all of the data produced is properly collected with an appropriate environmental reference corrector, **a)** the 'marginal' training sets will need to be reevaluated by the classifying analyzer before each use to verify the 'classification' accuracy of such analyzers and **b)**, periodically, the in-process 'wet test' will need to be performed on batch-representative in-process samples to confirm the accuracy of such analyzers' findings."

"Finally, to comply with CGMP (21 CFR 211.165(d)), release testing must be done on representative samples from each batch — when the process analyzer

does not test (e.g., NIR spectroscopy systems), the manufacture is still required to perform the requisite release testing."

"In some cases, this approach may be too burdensome and may discourage the use of some new technologies (e.g., use of acoustic ~~measurement~~ *evaluation* patterns or 'signatures' for ~~process~~ *in-process* controls)."

"~~An emphasis on~~ *Accumulated* process knowledge *derived from appropriate batch-representative test data for each variable factor in each batch* can, in many cases, ~~provide less burdensome approaches for validating~~ *greatly reduce the burden for defining the requisite training sets, performing the requisite training, and verifying the suitability of the* new technologies for their intended use."

41 Page "16"

Lines "521—524" – "Transfer of *a current* laboratory analytical *test* methods *(e.g., an HPLC method for content)* to *a comparable* in-line or at-line *test* methods *(e.g., an automated sample-preparation [sampling, weighing and dilution] UV/Visible test system for content)* using test-to-test comparisons may not necessitate a PAT approach."

"Existing regulatory and compendial approaches and guidances on analytical method validation should be considered *in such cases."*

42 Page "16"

Lines "526—534" – "Structured product and process development on a small scale, using experiment design and an on- or in-line process analyzer to collect data in real time for evaluation of kinetics on reactions and other processes such as crystallization and powder blending can provide valuable insight and understanding for process optimization, scale-up, and technology transfer."

"~~Process~~ *The maturation of such firms' process* understanding then continues in the production phase ~~when possibly~~ where other variables (e.g., environmental and supplier changes) may be encountered."

"Therefore, continuous learning through data collection and analysis over the life cycle of a product is important."

43 Page "16"

Lines "538—546" – "Within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product *provided the components, environmental conditions, equipment, and process steps are adequately controlled.*"

"For processes that are well understood, *well controlled and CGMP-compliant,* opportunities exist to develop less restrictive regulatory approaches to manage change."

"Thus, a focus on process understanding, *control and compliance* can facilitate risk-based regulatory decisions and innovation."

"Note that risk analysis and management is broader than what is discussed within the PAT framework and may form a system of its own."

"This is currently under discussion as part of the broad FDA Risk-Based initiative."

44 Page "16"

Lines "500—557" – "The fast pace of innovation in today's information age necessitates integrated systems thinking for ~~evaluating~~ *the in-depth evaluation* and timely application of efficient *CGMP-compliant* tools and systems that satisfy the needs of *all of the* patients and the industry."

"Many of the advances that have occurred, and are anticipated to occur, are bringing the development, manufacturing, quality assurance, and information/knowledge management functions so closely together that these four areas should be coordinated in an integrated manner *that is fully CGMP-compliant as well as compliant with 21 CFR Part 11*."

"Therefore, upper management support for these initiatives is critical for *their* successful implementation."

45 Pages "16—17"

Lines "561—571" – "~~*Real-time*~~ *Given the requirement that all drugs must be CGMP-compliant, near-real-time release* is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on the *on-line, electronic, QCU review and acceptance of the* process analytical *evaluation and* ***test*** data."

"Typically, the PAT component of ~~*real-time*~~ *near-real-time release* can include a validated combination of assessed material ~~attributes~~ *characteristics* (in-process and/or product ~~at final process stage~~), process controls, process end-points, *CGMP-required test data and test data assessments*, and other critical process parameters."

"~~Material~~ *While in-process* ~~attributes~~ *variable factors* can be assessed using direct and/or indirect (e.g., correlated) process analytical methods, **a)** *the CGMP regulations explicitly require identity testing on lot-shipment representative samples and test result acceptance for incoming components (21 CFR 211.84(b), 21 CFR 211.84(d) and 21 CFR 211.160(b)(2)), and* ***b)****, for drug product release, CGMP requires the use of statistical-quality-control-based* ***testing*** *of batch-representative sample units and states that* **"statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels"** *(21 CFR 211.165(d))."*

"Thus, whatever a regulated firm elects to do, the aforementioned evaluations must include the explicitly required testing (not just evaluations correlated thereto) for incoming component acceptance and drug-product release."

"The combined process analytical ~~measurements~~ *evaluations (including classification or examination outcomes)* and other *CGMP-mandated* test data gathered during the manufacturing process can serve the basis for ~~*real-time*~~ *the near-real-time release* of the final product ~~and would demonstrate~~ *that demonstrates* that each batch conforms to established regulatory ~~quality attributes~~ *requirements*."

~~"We consider real time release testing to be an example of alternative analytical procedures for final product release."~~

Based on the CGMP regulations, the preceding statement ignores clear regulations that state otherwise.

In addition to the preceding requirements, the CGMP regulations clearly require the firm's quality control unit to perform the release after reviewing the data.

Based on the preceding, there can be no real-time release, the best that can be attained and comply with CGMP is near-real-time release.

Furthermore, in 1988, the US Supreme Court ruled that no FDA administrator has the right to ignore any clear regulation. [**Note:** The US Supreme Court in a case involving attempts by the EPA to ignore a clear EPA regulation recently affirmed this general position concerning administrator authority vis-à-vis the mandate of a clear regulation.]

In addition, that ruling held that a firm could not use such administrative "guidance" (a letter from the FDA in that instance) as a defense when the firm acts in a manner that violates a clear regulation.

Thus, publishing non-CGMP-compliant guidance is also a disservice to the industry.

Given the preceding and the amendments added to the FDA Act by Congress in the 1990's, this reviewer strongly recommends that this Draft be corrected to reflect the preceding realities.

46 Page "17"

Lines "573—578" – " ~~"*Real time release* as defined in this guidance builds on parametric release for heat terminally sterilized drug products, a practice in the United States since 1985."~~

~~In real time release, material attributes are measured and controlled along with process parameters.~~

~~Real time release as defined in this guidance may fulfill the requirements of parametric release for all dosage forms as defined by other regulatory authorities.[4]~~

~~"[4] Note for Guidance on Parametric Release issued by the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP/QWP/30 15/99, 1 March 200 1, London).~~"

For the same reasons stated in the justification for the changes proposed in the previous paragraph and the fact that, as proposed, the text is anti-quality, this reviewer recommends that this paragraph and footnote be removed from the guidance.

47 Page "17"

Lines "580—586" – "The Agency's approval should be obtained prior to implementing ~~*real time*~~ *near-real-time release* for final products."

"Process understanding, control strategies, plus on-, in-, or at-line ~~measurement~~ *evaluation* of critical ~~attributes~~ *variable factors* that relate to product quality can provide a scientific risk-based approach to justify how ~~*real time*~~ *near-real-time* quality assurance *augmented by the requisite CGMP testing* may be equivalent to, or better than, *the prevalent* laboratory-*only*-based testing ~~on~~ *and quality-control-unit test result assessment* on today's collected samples."

"~~Real-time~~ Near-real-time release as ~~defined~~ *outlined* in this guidance ~~meets~~ *can meet* the requirements of testing and release for distribution (21 CFR 211.165) *provided the explicit CGMP requirements are met for:* ***a)*** *an identity* ***test*** *on representative samples of each shipment of each lot of each incoming component acceptance (21 CFR 211.84) and* ***b)*** *a statistical quality control test and test acceptance assessment against appropriate AQL criteria are conducted on an appropriate number of batch representative units from each batch (21 CFR 211.165(d)).*"

48 Page "17"

Lines "588—591" – " With ~~*real-time*~~ *near-real-time* quality assurance, the desired ~~quality attributes are~~ process performance and material acceptability can be ensured ~~through~~ *using* ~~continuous~~ *CGMP-compliant, near-real-time* assessment during *the* manufacture *of each batch.*"

"~~Data~~ *As required by 21 CFR 211.110, the test and evaluation data* from production batches can still serve ~~to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch~~ "to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

49 Page "17"

Lines "595—602" – "The Agency understands that to enable successful implementation of PAT, flexibility, coordination, and communication with manufacturers is critical."

"The Agency believes that current regulations are sufficiently broad to accommodate these new strategies."

~~Regulations can effectively support innovation (e.g., new drugs and drug delivery systems) as long as clear communication mechanisms exist between the Agency and industry, for example, in the form of meetings or informal communications between the Agency and manufacturers during drug development.~~

Since the CGMP regulations being discussed in this guidance consist of clear requirements that, in most cases, do not restrict the regulated firm to any one *scientifically sound* and *appropriate* approach to meeting the requirement ***minimums*** established, the regulated firms are, except in a few cases, free to use any *scientifically sound* and *appropriate* approach appertaining thereto.

However, the firms must prove that the approach they are using meets the applicable CGMP requirements including the CGMP requirement that the approaches used must be *scientifically sound.*

In the case of 21 CFR 211.165(d), "Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels," the regulations mandate **testing** not *classifying*, "statistical quality control criteria," and the "statistical quality control criteria" that must include "appropriate acceptance levels and/or appropriate rejection levels."

Similarly, 21 CFR 211.84 requires that the firm perform an "**identity test**" and, therefore, does not permit a CGMP-compliant firm to substitute an *identity classification* or, for that matter, one or more of the **USP** "IDENTIFICATION" tests (as some firms seem to be doing) in lieu of performing the required "**identity test**" on representative samples from "**each shipment of each lot**" of components.

In these two cases, each sample must be tested – PAT analyzers that classify the samples do not test them.

Thus, in these two cases, while such PAT analyzers may be used to augment the tests required, they cannot legally be used in lieu of the required tests.

50 Pages "17—18"

Lines "604—614" – "The first component of the PAT framework described above addresses many of the uncertainties with respect to new technologies and outlines broad principles for addressing anticipated scientific and technical issues."

"This information should assist a manufacturer who is proposing to the Agency innovative technologies that may seem to call for a new regulatory ~~path~~ *direction*."

"The Agency encourages such proposals and has developed new regulatory strategies to consider such proposals."

"The Agency's new regulatory strategy includes (1) a PAT team approach for CMC review and CGMP inspections; (2) joint training and certification of PAT review, inspection and compliance staff; (3) scientific and technical support for the PAT review, inspection and compliance staff; and (4) the recommendations provided in this guidance."

51 Page "18"

Lines "616—623" – "The recommendations provided in this guidance are intended to alleviate the fear of delay in approval as a result of introducing new manufacturing technologies."

"Ideally, PAT principles and tools should be introduced during the development phase."

"The advantage of using these principles and tools during development is to create opportunities to improve the mechanistic basis for establishing regulatory specifications."

"Manufacturers are encouraged to use the PAT framework to develop and discuss approaches for establishing mechanistic-based *CGMP-compliant* regulatory specifications for their products."

52 Page "18"

Lines "625—632" – "We also encourage the use of PAT strategies for the manufacture of currently approved products."

"Manufacturers may want to evaluate the suitability of a PAT tool on experimental and/or production equipment and processes."

"For example, when evaluating experimental on- or in-line process analyzers during production, it is recommended that risk analysis ~~of the impact~~ *be used to assess the potential adverse impacts, if any,* on product quality ~~be conducted~~ before installation *is initiated."*

"This can be accomplished within the facility's quality system without prior notification to the Agency."

"Data collected using an experimental tool should be considered research data."

53 Page "18"

Lines "634—646" – "When using new ~~measurement~~ *evaluation* tools, such as on/in-line process analyzers, certain data trends that may be intrinsic to the current acceptable process may be observed."

"Manufactures should scientifically evaluate these data to determine how, or if, such trends *adversely* affect quality and/or the implementation of *the* PAT tools *being studied.*

"In cases that the data observed clearly indicate an underlying process control problem, that problem must be investigated in the same manner as required for any other such problem."

"*Except where it is part of a CGMP-mandated problem investigation, the* FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tools."

"The FDA's ~~routine~~ general inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods)."

"Any FDA decision to inspect research data would be based on their being: **a)** part of a problem investigation or **b)** exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.300.[5]"

"[5] FDA/ORA Compliance Policy Guide, Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG 7151.02)"

"Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner."

54 Pages "18—19"

Lines "651—658" – "One goal of this guidance is to tailor the Agency's usual regulatory scrutiny to meet the needs of PAT-based innovations that (1) improve the scientific basis for establishing regulatory specifications, (2) promote continuous improvement, and (3) improve manufacturing while maintaining or improving the current level of product quality assurance."

"To ~~be able to do this~~ *facilitate that goal,* manufacturers should communicate important scientific knowledge to the Agency and resolve related technical issues in a timely manner."

"~~Our~~ *The Agency's* goal is *also* to facilitate a flexible regulatory assessment involving multiple Agency offices with varied responsibilities."

55 Page "19"

Lines "660—668" – "This guidance provides a broad perspective on ~~our~~ *the Agency's* proposed PAT regulatory approach."

"Close communication between the manufacturer and the Agency's PAT review and inspection staff will be a key component in this approach."

"We anticipate that*: a)* communication between manufacturers and the Agency will continue over the life cycle of a product and *b)* that communication will be in the form of meetings, telephone conferences, and written correspondence."

"Any written correspondence should be identified clearly as Process Analytical Technology or PAT."

"All marketing applications, amendments, or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner."

56 Page "19"

Lines "670—684" – "We recommend general correspondence related to PAT be directed to our new FDA PAT Team."

"Manufacturers can also contact the PAT Team regarding any PAT questions or issues related to nonapplication drug products or not pertaining to a specific submission or application at the address below.

FDA Process Analytical Technology Team
Office of Pharmaceutical Science, HFD-003
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857"

"~~For currently approved products, during their planning phase, manufacturers should consider the effects of PAT on the current process, in-process controls, and specifications~~."

This reviewer recommends either deleting this sentence as the reviewer has done or replacing it with clear text that addresses both a) approved product processes whose initial full-scale implementation is pending (where the phrase "during their planning phase" makes sense) and b) approved product processes that i) have been in use for some time and ii) are being reviewed as a part of the firm's annual-review process (where the phrase "during their planning phase" makes no sense).

"When consulting with the Agency, manufacturers may want to discuss not only specific PAT plans, but also *their* thoughts on a possible *CGMP-compliant* regulatory path *to implementing those plans.*"

57 Page "19"

Lines "686—693" – "This guidance is also intended to encourage research to explore suitability and validation strategies for new technologies prior to planning and implementing PAT-based manufacturing."

"If research is conducted in a production facility, it should be *conducted* under the facility's ~~own~~ *existing CGMP-compliant* quality system."

"Information generated from this research along with other information that provides process understanding can be used to formulate and communicate implementation plans to Agency staff."

"Plans for implementing and regulatory assessment of PAT can be agreed to with the Agency through a variety of communication channels."

58 Pages "19—20"

Lines "695—700" – "Section 116 of the 1997 Food and Drug Administration Modernization Act amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes."

"We recommend that manufacturers continue to consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change.[6]"

"[6] FDA/CDER guidance for industry Changes to an Approved NDA or ANDA."

59 Page "20"

Lines "702—719" – "In general, PAT implementation plans should be risk based."

"We are proposing the following possible implementation options:

- PAT can be implemented under the *CGMP-compliant* facility's quality system; CGMP inspections by the Agency *will* follow.
- PAT can be implemented following *an acceptable* CGMP inspection by the PAT Team. The PAT Team can assist manufacturers with pre-operational review of the PAT manufacturing facility and process (ORA Field Management Directive NO. 135).[7]

  "[7] FDA Field Management Directive 135. http://www.fda.gov/ora/inspect-ref/fmd135a.html"

  "The recommendations in the inspection report will: *a)* serve as a summary basis ~~of~~ *in the Agency's* final *review and* approval of the process and *b)* be filed in the relevant application, where needed, ~~and~~ *as well as the* facility databases within the Agency."
- A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT Team or PAT certified investigator before implementation.
- A comparability protocol[8] can be submitted to the Agency outlining PAT research, validation and implementation strategies and time lines.

"[8] FDA draft guidance for industry, Comparability Protocols — Chemistry, Manufacturing, and Controls Information, issued February 2003. Once finalized, it will represent the Agency's current thinking on this topic."

"Following approval of this comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation."

60 Page "20"

Lines "720—723" – "It should be noted that when certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered.

"~~manufactures~~ *Manufacturers* should evaluate and discuss with the Agency the most appropriate option for their situation.

61 Page "21"

Line "728" – Insert after **Line 728**, the following:

"***1. ANSI/ASQ/ASQC/BSR/IEC/ISA/ISO Standards***

STATISTICS

General

ANSI/ISO/ASQC A3534-1-1993: Statistics - Vocabulary and Symbols - Probability and General Statistical Terms -

ANSI/ISO/ASQC A3534-2-1993: Statistics - Vocabulary and Symbols - Statistical Quality Control

ISO 3534-1:1993 Statistics -- Vocabulary and symbols -- Part 1: Probability and general statistical terms

ISO 3534-2:1993 Statistics -- Vocabulary and symbols -- Part 2: Statistical quality control

ISO 3534-3:1999 STATISTICS -- VOCABULARY AND SYMBOLS -- PART 3: DESIGN OF EXPERIMENTS

Interpretation of Data

ISO 2602:1980 Statistical interpretation of test results -- Estimation of the mean -- Confidence interval

ISO 2854:1976 Statistical interpretation of data -- Techniques of estimation and tests relating to means and variances

ISO 3207:1975 Statistical interpretation of data -- Determination of a statistical tolerance interval & ISO 3207:1975/Add 1:1978

ISO 3301:1975 Statistical interpretation of data -- Comparison of two means in the case of paired observations

ISO 3494:1976 Statistical interpretation of data -- Power of tests relating to means and variances

ISO 5479:1997 Statistical interpretation of data -- Tests for departure from the normal distribution

ISO 5725-1:1994 Accuracy (trueness and precision) of measurement methods and results -- Part 1: General principles and definitions & ISO 5725-1:1994/Cor 1:1998

ISO 5725-2:1994 Accuracy (trueness and precision) of measurement methods and results -- Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method & ISO 5725-2:1994/Cor 1:2002

ISO 5725-3:1994 Accuracy (trueness and precision) of measurement methods and results -- Part 3: Intermediate measures of the precision of a standard measurement method & ISO 5725-3:1994/Cor 1:2001

ISO 5725-4:1994 Accuracy (trueness and precision) of measurement methods and results -- Part 4: Basic methods for the determination of the trueness of a standard measurement method

ISO 5725-5:1998 Accuracy (trueness and precision) of measurement methods and results -- Part 5: Alternative methods for the determination of the precision of a standard measurement method

ISO 5725-6:1994 Accuracy (trueness and precision) of measurement methods and results -- Part 6: Use in practice of accuracy values & ISO 5725-6:1994/Cor 1:2001

ISO 16269-7:2001 Statistical interpretation of data -- Part 7: Median -- Estimation and confidence intervals

Control Charts

ANSI/ASQC B1-B3-1996: Quality Control Chart Methodologies

ISO 7870:1993 Control charts -- General guide and introduction

ISO/TR 7871:1997 Cumulative sum charts -- Guidance on quality control and data analysis using CUSUM techniques

ISO 7873:1993 Control charts for arithmetic average with warning limits

ISO 7966:1993 Acceptance control charts

ISO 8258:1991 Shewhart control charts & ISO 8258:1991/Cor 1:1993

Other

ISO/TR 10017:2003 Guidance on statistical techniques for ISO 9001:2000

ISO 10576-1:2003 Statistical methods -- Guidelines for the evaluation of conformity with specified requirements -- Part 1: General principles

ISO 11453:1996 Statistical interpretation of data -- Tests and confidence intervals relating to proportions & ISO 11453:1996/Cor 1:1999

ISO 11462-1:2001 Guidelines for implementation of statistical process control (SPC) -- Part 1: Elements of SPC

ISO/TR 13425:1995 Guide for the selection of statistical methods in standardization and specification

INSPECTION STANDARDS (Sampling and Testing or Examination)

Sampling

ISO 11648-1:2003 Statistical aspects of sampling from bulk materials -- Part 1: General principles

ISO 11648-2:2001 Statistical aspects of sampling from bulk materials -- Part 2: Sampling of particulate materials

ISO 10725:2000 Acceptance sampling plans and procedures for the inspection of bulk materials

Attribute

ANSI/ASQC S2-1995: Introduction to Attribute Sampling

ANSI/ASQC Z1.4-1993: Sampling Procedures and Tables for Inspection by Attributes

ASQC Q3-1988: Sampling Procedures and Tables for Inspection of Isolated Lots by Attributes

ISO 2859-0:1995 Sampling procedures for inspection by attributes -- Part 0: Introduction to the ISO 2859 attribute sampling system

ISO 2859-1:1999 Sampling procedures for inspection by attributes -- Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection & ISO 2859-1:1999/Cor 1:2001

ISO 2859-2:1985 Sampling procedures for inspection by attributes -- Part 2: Sampling plans indexed by limiting quality (LQ) for isolated lot inspection

ISO 2859-3:1991 Sampling procedures for inspection by attributes -- Part 3: Skip-lot sampling procedures

ISO 2859-4:2002 Sampling procedures for inspection by attributes -- Part 4: Procedures for assessment of declared quality levels

ISO 8422:1991 Sequential sampling plans for inspection by attributes & ISO 8422:1991/Cor 1:1993

Variables

ANSI/ASQC Z1.9-1993: Sampling Procedures and Tables for Inspection by Variables for Percent Nonconforming

BSR/ASQ Z1.9-2003: Sampling Procedures and Tables for Inspection by Variables for Percent Nonconforming

ISO 3951:1989 Sampling procedures and charts for inspection by variables for percent nonconforming

ISO 8423:1991 Sequential sampling plans for inspection by variables for percent nonconforming (known standard deviation) & ISO 8423:1991/Cor 1:1993

ISO/TR 8550:1994 Guide for the selection of an acceptance sampling system, scheme or plan for inspection of discrete items in lots

DETECTION & CALIBRATION

Detection

ISO 11843-1:1997 Capability of detection -- Part 1: Terms and definitions

ISO 11843-2:2000 Capability of detection -- Part 2: Methodology in the linear calibration case

ISO 11843-3:2003 Capability of detection -- Part 3: Methodology for determination of the critical value for the response variable when no calibration data are used

Calibration

ANSI/ASQC M1-1996: American National Standard for Calibration Systems

ISO 11095:1996 Linear calibration using reference materials

ISO Guide 32:1997 Calibration in analytical chemistry and use of certified reference materials

ISO 12713:1998 Non-destructive testing -- Acoustic emission inspection -- Primary calibration of transducers

ISO 12714:1999 Non-destructive testing -- Acoustic emission inspection -- Secondary calibration of acoustic emission sensors

REFERENCE STANDARD MATERIALS

ISO Guide 30:1992 Terms and definitions used in connection with reference materials

ISO Guide 31:2000 Reference materials -- Contents of certificates and labels

ISO Guide 33:2000 Uses of certified reference materials

ISO Guide 34:2000 General requirements for the competence of reference material producers

ISO Guide 35:1989 Certification of reference materials -- General and statistical principles

GENERAL QUALITY SYSTEM RELATED

ANSI/ISO/ASQC Q10011-1994 Series: Guidelines for Auditing Quality Systems

ANSI/ASQC E2-1996: Guide to Inspection Planning

ANSI/ISO/ASQC Q10006-1997: Quality Management - Guidelines to Quality in Project Management

ANSI/ASQ Z1.13-1999: Quality Systems Guide for Research

ANSI/ISO/ASQC Q9003-1994: Model for Quality Assurance in Final Inspection and Test

ASQC Q2-1991: Quality Management System and Elements for Laboratories - Guidelines

ANSI/ISO 17025-1999 General Requirements for the Competence of Testing and Calibration Laboratories

RISK MANAGEMENT

ISO/IEC Guide 73:2002 Risk management -- Vocabulary -- Guidelines for use in standards

ISO 14971:2000 Medical devices -- Application of risk management to medical devices

OTHER

ANSI/IEC/ASQC D601123-1997: Reliability Testing - Compliance Test Plans for Success Ratio

ANSI/IEC/ASQC D601070-1997: Compliance Test Procedures for Steady-State Availability

ISA-TR91.00.02-2003: Criticality Classification Guideline for Instrumentation

62 Page "21"

Lines "729—752 " – "~~*1. ASTM Standards*~~ ***2. ASTM Standards***"

"D 3764 - 0 1: Standard Practice for Validation of Process Stream Analyzer Systems.

D 6624-01: Standard Practice for Determining a Flow-Proportioned Average Property Value (FPAPV) for a Collected batch of Process Stream Material Using Stream Analyzer Data

D 4855 - 97: Standard Practice for Comparing Test Methods.

D 6299 - 02: Standard Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance.

E 178 - 02: Standard Practice for Dealing with Outlying Observations.

E 1655 - 00: Standard Practices for Infrared Multivariate Quantitative Analysis.

E 1866 - 97: Standard Guide for Establishing Spectrophotometer Performance Tests,

E 13 1-OOa: Standard Terminology Relating to Molecular Spectroscopy

E 456-02: Standard Terminology Relating to Quality and Statistics"

63 Page "21"

Line "754—756" – "~~2. International Society of Pharmaceutical Engineers~~ ***3. International Society of Pharmaceutical Engineers***"

GAMP Guide for Validation of Automated Systems, issued on December 2003"

64 Page "21"

Line "758—762" – "~~3. Parenteral Drug Association~~ ***4. Parenteral Drug Association***"

"PDA. May/June 2000. Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods. PDA Journal of Pharmaceutical Science and Technology 54(3) Supplement TR33"

Reviewer's Concluding Observations

In addition to the deficiencies in addressing the "CGMP ***minimums***" issues associated with incoming components, in-process materials and controls, and drug product acceptance for release discussed by this reviewer, this Drafts fails to address, or inadequately addresses CGMP-complinace issues associated with the following regulations (listed in the order they appear in the CGMP for drug products (21 CFR Part 211 with the **bolding** emphasis added for the more critical CGMP requirement ***minimums*** with which this guidance should be congruent):

1. "Sec. 211.22 Responsibilities of quality control unit.
   (a) **There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.**
   (b) ...
   (c) ...
   (d) ..."

2. "Sec. 211.67 Equipment cleaning and maintenance.
   (a) **Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.**
   (b **Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:**
      (1) Assignment of responsibility for cleaning and maintaining equipment;
      (2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
      (3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
      (4) Removal or obliteration of previous batch identification;
      (5) Protection of clean equipment from contamination prior to use;
      (6) Inspection of equipment for cleanliness immediately before use.
   (c) **Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in Sees. 211.180 and 211.182."**

3. "Sec. 211.68 Automatic, mechanical, and electronic equipment.
   (a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.
   (b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related

system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained."

4. "Sec. 211.100 Written procedures; deviations.
   (a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
   (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."

5. "Sec. 211.105 Equipment identification.
   (a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.
   (b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code."

6. "Sec. 211.113 Control of microbiological contamination.
   (a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.
   (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

7. "Sec. 211.134 Drug product inspection.
   (a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
   (b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
   (c) Results of these examinations shall be recorded in the batch production or control records."

8. "Sec. 211.160 General requirements.
   (a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified."

9. 21 CFR 211.160(b)(4), "The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision

limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used."

10. "Sec. 211.167 Special testing requirements.
    (a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.
    (b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.
    (c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed."

11. "Sec. 211.182 Equipment cleaning and use log.
    A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order."

12. "Sec. 211.184 Component, drug product container, closure, and labeling records.
    These records shall include the following:
    (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in Sec. 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.
    (b) The results of any test or examination performed (including those performed as required by Sec. 211.82(a), Sec. 211.84(d), or Sec. 211.122(a)) and the conclusions derived therefrom.
    (c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.
    (d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with Secs. 211.122(c) and 211.130(c).
    (e) The disposition of rejected components, drug product containers, closure, and labeling."

13. "Sec. 211.186 Master production and control records.
    (a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.
    (b) Master production and control records shall include:
        (1) The name and strength of the product and a description of the dosage form;
        (2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;
(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
(5) A statement concerning any calculated excess of component;
(6) A statement of theoretical weight or measure at appropriate phases of processing;
(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to Sec. 211.192 is required;
(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed."

14. "Sec. 211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:
(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;
(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:
(1) Dates;
(2) Identity of individual major equipment and lines used;
(3) Specific identification of each batch of component or in-process material used;
(4) Weights and measures of components used in the course of processing;
(5) In-process and laboratory control results;
(6) Inspection of the packaging and labeling area before and after use;
(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
(8) Complete labeling control records, including specimens or copies of all labeling used;
(9) Description of drug product containers and closures;
(10) Any sampling performed;
(11) Identification of the persons performing and directly supervising or checking each significant step in the operation;
(12) Any investigation made according to Sec. 211.192.
(13) Results of examinations made in accordance with Sec. 211.134."

15. "Sec. 211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup."

The overall impression left with this reviewer is that those who drafted this guidance should spend more time learning what CGMP requires vis-à-vis the acceptance inspection (sampling and testing) requirements for lot-or batch-representative samples of: **a)** each shipment of each lot of each in-coming component and **b)** each batch of drug-product (which requires the use of statistical quality control for batch acceptance for release).

Further the statistics-based (21 CFR 211.110(b)) in-process material acceptance inspection (of batch-representative samples [21 CFR 211.160(b)(2)] from each batch) must monitor and validate "**the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**" (21 CFR 211.110(a)).

In all cases, release cannot be automatic <u>because</u> the quality control must review the records and findings appertaining thereto, and approve the acceptance or rejection of: **a)** each shipment of each lot of each component, **b)** each batch or lot of each in-process material at the end of each phase of manufacture, and **c)** each batch or lot of drug product.

Additionally, more study of the fundamentals of inspection science is needed as well as study into the proper terminology to use with respect to on-, in-, at- or off- line analysis systems that examine and classify samples rather than test and quantify one of more of the samples' variable factors.

Finally, this reviewer would recommend that all parties should improve their understanding of the fundamentals tenets of population statistics and distribution as they impact the setting of *scientifically sound population-representative*:

- Acceptance inspection plans and
- Acceptance specifications

Both *non-discrete* pharmaceutical components and materials (for which there are no explicitly applicable consensus standards) and *discrete* (units) pharmaceutical drug-products (for which there are recognized consensus standards for both attribute examinations and variables testing) should be studied.