

FACILITY AUTOMATION MANAGEMENT ENGINEERING (FAME) SYSTEMS

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Friday, 18 June 2004

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

RE: Docket No. 04N-0181

FORMAL COMMENTS ON:

"Critical Path Initiative; Establishment of Docket"

Pursuant to a "request for comment" in *FEDERAL REGISTER*, Vol. 69, No. 78, pp 21839 – 21840.

BACKGROUND

After an initial reading and a rereading of the FDA's white paper, "*Innovation Stagnation Challenge and Opportunity on the Critical Path to New Medical Products*" and a thoughtful reading of the notice soliciting comment in the Federal Register, FAME Systems offers the comments that follow.

The comments provided are based on decades of hands on experience in the development of drug products and their manufacturing processes and controls (API and dosage form), the initial conformance assessment of drug products, and the in-depth control of the ongoing manufacturing of drug products in a variety of delivery formats including, in order of experience, tablets, capsules, powders for reconstitution, liquids, creams, ointments, metered-dose inhalers, and patches.

To clearly separate **FAME Systems'** review statements from the FDA's statements, **FAME Systems'** comments are in an **Arial** or **italicized Arial** font and the basis statements are in a **Times New Roman** or other font like that used by the FDA.

When either a binding regulation or a statute is quoted, the text is in a **Lydian** font.

When other recognized sources are quoted, a **Perpetua** font is used.

Should anyone who reads these comments find that their guidance is at odds with sound science or the applicable statutes and/or regulations, or that additional clarification is needed in a given area, then, in addition to providing the sound science or rationale that refutes the comment text provided, or his or her clarifying comments to the public docket, he or she is asked to e-mail drking@dr-king.com a copy of that sound science, rationale, and/or commentary.

Respectfully,

Dr. King

INTRODUCTION

These comments begin by reviewing the FDA's whitepaper's stated positions and, from this commenter's view, the validity, or lack thereof, of said positions.

To facilitate the Agency's review of the comments provided, this commenter quotes the FDA's text before commenting thereon.

The comments provided are based on the commenter's personal knowledge, experience, and understanding of the state of affairs in the pharmaceutical industry.

Where appropriate, the comments will be supported by reference to applicable statute and/or regulation that sets forth requirements that the medical products industry and, in some instances, the FDA have apparently decided to knowingly ignore but which are critical to the providing of safe and efficacious medical products to the public.

This commenter will begin by reviewing and commenting on the background document, "INNOVATION/STAGNATION: Challenge and Opportunity on the Critical Path to New Medical Products."

Then, this commenter will provide this commenter's cogent remarks in response to the Agency's request for "input in identifying and prioritizing the most pressing medical product development problems, and the areas that provide the greatest opportunities for rapid improvement and public health benefits."

With all the preceding in mind, let us proceed to examine the Agency's background document.

"INNOVATION/STAGNATION:

Challenge and Opportunity on the Critical Path to New Medical Products

EXECUTIVE SUMMARY

This report provides the Food and Drug Administration's (FDA's) analysis of the *pipeline problem* — the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients."

Without providing any substantiating rationale other than raw statistical plots of non-inflation-corrected spending increase, apparent short-term decreases in the total number of original NMEs and BLAs submitted to the FDA, and putative similar trends at "regulatory agencies worldwide," the FDA first postulates a "*pipeline problem*" and then asks for innovative ways to facilitate the submission of more NMEs and BLAs to address this Agency "problem."

Further, the FDA ignores the fact that the Agency's actions to date to facilitate the submission of more NMEs and BLAs have resulted in an

increasing number of; **a)** approved then withdrawn, **b)** “black box” warnings **and c)** restrictions on the prescribing said medical products as well as the increasing knowing and willful non-compliance upon the part of the major players in the pharmaceutical industry.

These non-compliances have only been partially addressed by the rise in the number and cost of the consent decrees and product withdrawals for cause after the Agency, *in its zeal to facilitate the review and the “risk based” approval of said products*, approved products: **a)** that cause more harm than good, **b)** whose safety spectrum is much narrower than the data submitted for the approval indicated, **and/or c)** whose actual manufacturing controls were knowingly violative.

Moreover, the Agency’s analysis also ignores the reality that part of the decrease is tied to the industry’s conscious and knowing decision to pursue medical products that diagnose, mitigate and treat illnesses at the expense of medical products that prevent or cure.

For example, though the science clearly indicates that HPV 16 and HPV 18 are linked to the initiation of cervical cancer, the 100% effective vaccine (based on a clinical trial in Europe) for these viruses is not being “fast tracked” even though said vaccine, if administered to young teens of both sexes before they become sexually active with a booster every ten years, could probably cure what are obviously sexually transmitted viral diseases that are at least a key part of the triggering mechanism for the majority of the cervical cancer in susceptible females (and there is some recent evidence that these same HPV viruses are implicated in prostate cancer).

Given the loss of revenue from all the treatment and mitigation products to the pharmaceutical industry and the loss of income from all of the cervical cancer surgeries and reduced PAP smear testing to the medical industry, it is easy to see why this cure is suppressed in favor of more and better “treatment.”

Or consider the approved, and then withdrawn, “Lyme Disease” vaccines that, *instead of being an effective treatment*, worsened the health of many who received them and, *for a time*, supplanted the effective curative antibiotic treatment that was effective in the majority of cases and, *unlike the vaccines*, did not irreparably harm the patients at any appreciable incidence level – *the pharmaceutical industry not only profited from these vaccines but also from the medical products needed to treat all those damaged by the vaccines for the rest of their lives* – a win-win “solution” for both the pharmaceutical and the medical industries – a lose-lose reality for both most of those who were vaccinated and the general public.

Moreover, many of these original NMEs and BLAs are competitor “me too” submissions that, *contrary to the Agency’s portrayal*, do not represent any breakthrough in technology or medical care.

Factually, other than the need to: **a)** reallocate its resources to better address its legal mandates (*such as performing not less than a biannual CGMP inspection of all facilities*) **and b)** better protect the public from the industry (*that, based on its admitted defrauding of both the Federal and State governments and its knowing willful CGMP non-compliances, is inherently unethical*), there is no “*pipeline problem*.”

For example, in the May/June issue of ***Pharmaceutical Engineering***, **24(3)**, in an article entitled, “The Real Capacity Crisis,” Jeff Odum reports, “Today, there are more than 400 biological products alone in clinical trials, and another 400 or so in preclinical trials” (page 116, column 1, paragraph 3).

Thus, the downturn reported by the Agency in BLAs will soon be replaced by a significant upturn in the number of BLAs filed – so much for the Agency’s putative submission “crisis.”

Furthermore, according to Mr. Odum, “As products continue to advance through the clinical approval process and vie for production capacity within the market place, there is one factor that stands as a ‘make or break’ proposition to the success of many companies. When a recent survey asked the question to 100 manufacturers of pharmaceutical products; ‘What will impact your company’s capacity over the next five years.’ More than 52% indicated a *lack of trained and experienced production staff* as their number one concern. Second was a *lack of trained and experienced scientific staff* as the greatest impact to capacity.”

Based on the biological industry’s view of its current status (as of 2004), there is no long-term declining BLA submission number “crisis” – though there may be an impending BLA submission overload crisis – and the rate-limiting issues on the BLA side are issues related to capacity and not the development-related issues postulated by the Agency.

“Today’s revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. This is because the current medical product¹ development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade. Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Developing products targeted for important public health needs (e.g., counterterrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging. In fact, with rising health care costs, there is now concern about how the nation can continue to pay even for existing therapies. If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.

¹ The term medical product includes drug and biological products as well as medical devices.”

Given the fact that the pharmaceutical industry’s supposed “developmental costs” and drug pricing are subject to manipulation by an unethical industry that is driven to maximize its profits at the expense of the public – and industry that increasingly spends more to advertise and entice use rather than to improve the quality of its products, no amount of innovation or technology should be expected to change their priorities from pursuing medical products that diagnose, treat, or mitigate at the expense of medical treatments that prevent or cure public health diseases and debilitating conditions.

Further until the public and the Agency stop the widening prescribing of drugs to larger populations based on questionable industry-designed studies against a placebo without any proven long-term benefit and with the minimization of the risks associated therewith, the aggregate cost of medical products will continue to rise much faster than not only inflation but also the “3X inflation” costing of the average drug product. [For example, estrogen replacement “therapy” to post menopausal women that finally independent studies have shown to have risks that, in general, outweigh their putative benefits. Yet these have not been withdrawn from the market – only the dose has been reduced on the “theory” that the benefits to the patient will outweigh the risks to the patient and with the certain knowledge that the pharmaceutical industry will benefit no matter what – after all, all of those with an excess risk of heart disease and cancer can easily be “treated” with other medical products and procedures – a win-win situation for both the pharmaceutical and medical industries.]

Moreover, as with all of the lessening of the Agency’s oversight in the areas of development and manufacturing over the past decade, all that pursuing initiatives that ease the submission process will do is to encourage the pharmaceutical industry to behave in increasingly less ethical ways in the future – minimally, the industry will be tempted to increasingly “blackmail” the FDA into pursuing ever riskier policies. [**Note:** On a recent “*60 Minutes*” episode, an industry spokesperson, speaking to the issue of decreasing research in the anti-infectives area, likened the development of a drug to that of a new automobile, stated that, like the automotive industry, the pharmaceutical industry intends to develop products that maximize profit (the public health be damned), and opined that, if new anti-infectives are needed, perhaps the government should pay for their development (perhaps like we do for military vehicles) – totally ignoring that, unlike the automotive industry, the pharmaceutical industry directly benefits from the billions spent on medical research (e.g., AZT and other anti-HIV drugs for HIV and AIDS).]

Factually, unless and until the government steps in and forces the medical industry to focus on the less lucrative, preventive and curative medical products, “the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health” because the treatment-oriented status quo is obviously much more profitable both short

term and long term than the alternative ever could be – like any “addictive” product – “every day for life” medical products are inexhaustible cash cows and, since all firms are both innovator and generic manufacturers, all benefit from them.

It is no coincidence that, since the 1970’s, many of the curative medical products have been developed in societies other than the US (Japan and Australia) where ethical behavior, personal integrity, and cure are valued other unethical behavior, greed, and treatment. [Note: Take, for example, the long road that the “curative” regimen for simple peptic ulcers took from the proof by an Australian researcher in 1982 that: **a) *Helicobacter pylori* (*H. pylori*)** was the causative agent **and b)**, *subsequently*, that a single treatment 14-day regimen with an acid blocker, an antibiotic to which the patient’s *H. Pylori* is susceptible, and Carafate had a 95+% cure rate (with virtually 100 % cure after a second course) to today’s most prescribed abbreviated regimen (dual antibiotic [Amoxicillin and Clarithromycin] and acid blocker [Prevacid®]) that is an “80-% effective in one course” treatment regimen that was approved in December of 1997 and has become widely used in this century (only after: **a)** the medical profession finally agreed on a “standard” treatment regimen in 1996 and **b)** the CDC finally undertook a program to educate the public that most ulcers are caused by a bacterium, ***H. pylori***, and can be cured with antibiotics {e.g., **in 1995, i)** the NIH found about 75 percent of ulcer patients are treated with antisecretory medications; **ii) only 5 percent receive the curative antibiotic therapy; and iii)** consumer research by the American Digestive Health Foundation found that nearly 90 percent of ulcer sufferers are unaware that ***H. pylori*** causes ulcers}) – “coincidentally,” this “cure” became “available” when the acid blocker became available OTC for “heart burn.” Moreover, by “requiring” an endoscopic examination with sampling and testing for ***H. pylori*** with a positive test for ***H. pylori*** prior to prescribing a curative regimen, “pushing for” repeat endoscopic examinations, and using a regimen with a single-regimen effective rate of “80 %” instead of the known 95+% effective one, the revenue stream to the medical specialist was preserved. Further, because of the “20%” need for a second curative regimen or more, or, *when that and the recommended alternate fail*, the patient’s being directed to use the palliative treatment regimen (acid blocker) for the rest of that patient’s lifetime, and the need to treat for complications arising from the required endoscopic examinations, both the pharmaceutical and medical industries have preserved a significant portion of their revenue stream. Yes, there is an ***H. pylori*** blood test but doctors still “insist” on the endoscopic exam with sampling and sample testing for ***H. pylori*** – it is a “better” procedure (“coincidentally” with a much higher profit) even though these same specialists resist: **a)** performing an “Antibiotic Susceptibility” screening test on the patient’s ***H. Pylori*** to identify the best antibiotic to use before initiating the treatment **and b)** extending the treatment beyond 14 days to 28 days. Moreover, *in spite of the availability of this cure*, some doctors still tend to prescribe a palliative “acid blocker” treatment regimen rather than one that has an “80%” probability of permanently curing the ***H. pylori*** infection. Finally, the best curative regimen continues to be unavailable to the patient.]

“What is the problem? In FDA’s view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The

new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures. Finally, the path to market even for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods.”-

A) Ignoring the reality that the pharmaceutical industry has deliberately chosen to operate in the manner that the FDA outlines as being a problem and **B)** failing to see the advantage that using cruder tools may accrue to the firm wishing to find a way to market a “me too” product that may have problems that modern tools would find before that medical product can be approved and marketed [because, in general, most marketed products are highly profitable even when, a few years later, their “hidden” problems emerge and force them off the market, or the Agency is convinced to leave them on the market even when the firm obtained the approval by committing fraud (knowingly failing to submit a key adverse study) to obtain the approval (e.g., Roche’s Accutane) – because the firms’ executive managers who make the decisions “know” that they won’t be prosecuted for their decisions no matter how many are maimed or die – **a)** the worst they expect from the government is a fine of “10 cents or less on the dollar of profit” (which they recover by raising their prices) and a consent decree – **and b)** the harm such products may do only provides further revenue from the medical products and procedures needed to address the damage caused (even when they lose, the win)], the Agency opines, “the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences.”

Without providing any substantiating evidence the Agency goes on to state, “developers have no choice but to use the tools and concepts of the last century to assess this century’s candidates. As a result, the vast majority of investigational products that enter clinical trials fail.”

If the pharmaceutical industry truly believed that it absolutely must have better “tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs,” then, the pharmaceutical industry, *having by far the greater scientific talent available to it (directly and indirectly)*, would, in many cases, have already developed and deployed such tools.

That the industry has deliberately chosen to ignore the deployment of said tools is indicative of this and any other knowledgeable scientist in the field

that the industry has its reasons for not actively pursuing the deployment of such tools even though, *based on what little is published*, such tools have been and are being developed. [Note: Like the automotive industry that is just now “deploying” hybrid cars (at a premium price) though the technology was “developed and proven” a decade ago, the pharmaceutical industry will only deploy such “better” tools when outside forces compel them to.]

According to the industry, the “high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures,” but, *having seen evidence that the prices for research intermediates and development are often highly inflated*, this commenter advise the Agency to take this industry rhetoric with a very large “grain of salt.”

As to the Agency’s last statement, “Finally, the path to market even for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods,” this commenter finds that deficiencies in the original screening methods and marketing and other management pressures contribute as much, if not more, to the “growing number of expensive failures” and “the long, costly and inefficient” path to market for “successful candidates” – especially for those that, because of “unexpected” (or, perhaps, unrevealed) adverse reactions, must or should be withdrawn after receiving approval.

In this commenter’s experience, firms often “hide” any evidence of “bad” news by:

- a. Presenting it in a transformed manner (e.g., grouping the data so that a bimodal distribution appears to be unimodal),
- b. Burying it in a ton of verbiage (e.g., on a single page in a 20+ page paragraph brimming with repetitive reporting of “good” news), **or**
- c. *As Roche and Biocraft (now Teva) did*, simply omitting the reporting of the problem issues from the information submitted to the Agency in the application even though the regulations clearly required reporting that adverse information.

Based on this commenter’s knowledge and experience, the process is as it is because the industry is comfortable with the status quo and all that the pharmaceutical industry is truly interested in is finding ways to “get away with” doing less and being less accountable for the harm that they knowingly do.

“A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. We need superior product development science to address these challenges — to ensure that basic discoveries turn into new and better medical treatments. We need to make the effort required to create better tools for developing medical technologies. And

we need a knowledge base built not just on ideas from biomedical research, but on reliable insights into the pathway to patients.”

If, as the FDA states, “A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product,” then, the FDA simply needs to issue regulations mandating the use of such within one year and thereby force the industry to deploy the technologies that they have been developing and studying for the past two decades or more.

Before addressing a need for “superior product development science to address these challenges — to ensure that basic discoveries turn into new and better medical treatments,” the Agency must mandate that the industry implement the existing fundamental development science and applicable scientific consensus standards that the industry currently is **knowingly** ignoring even when the use of such is required by statute and/or regulation.

Moreover, the Agency needs to issue regulations that will ensure that basic discoveries like *Helicobacter pylori*’s causing simple ulcers or the linking of HPV-16 and HPV-18 to cervical cancer will be **rapidly** turned into the most effective cures (e.g., antisecretory compound, the appropriate antibiotic and Carafate [not Pepto Bismol tablets or any generic Sulcralfate] for ulcers, and the 100% effective vaccine for HPV-16 and HPV-18, strongly linked to cervical cancer) and not delayed (as ulcer cure was for 15 years and the “100% effective” HPV vaccine is currently being delayed) or converted from cures into “new and better medical treatments” or less effective cures (antisecretory compound and antibiotic without Carafate for ulcers) that unnecessarily increase industry revenue and the cost of “healthcare” without any real benefit to public health.

“The medical product development process is no longer able to keep pace with basic scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path.”

This commenter knows of no empirical evidence that supports the Agency’s statement that ***“The medical product development process is no longer able to keep pace with basic scientific innovation.”***

From this commenter’s knowledge and experience, all that is needed is for the industry to deploy the tools they have been developing and/or to use the widely available best practical technologies that have long been available in the related chemical industries that produce biocides or other bioactive compounds. [For example, in 1970’s the biocides industry developed and implemented methods for the identification and determination of all components at the 0.1 % by weight or, if toxic, the appropriate lower level (down to the parts per

billion level) and to require more than retention-time match to assert that components eluting at the same time relative to standards are the same structures. Today, the FDA's "ICH-directed" position still: **a)** permits "HPLC area % using a UV/visible detector" to be used as the percentage guide even though the absorptivities of organic molecules are known to vary by more than 10 orders of magnitude and isomeric compounds have absorptivities that vary by up to 4 orders – rendering such area-% measurements highly suspect in the absence of identification of the structure of the impurity and **b)** rely on retention time match in evaluating the comparability of impurity profiles.]

Thus, all that is truly needed is regulations compelling the industry to: **a)** use the same modern technologies as the best practical technologies used in related industries **and b)** deploy the tools that it has been developing for the past decade.

"A new product development toolkit...is urgently needed to improve predictability and efficiency along the critical path."

This reviewer agrees with the Agency's position provided that that toolkit absolutely requires that all evaluations must be performed on samples that the firm has proven to be **batch representative** against **acceptance criteria** that have been established to be appropriately inside of the lifetime criteria required for the medical product. [Note: For discrete units, the minimum number of samples specified in the applicable procedure in the consensus standards, ANSI Z1.9 or ISO 3951, must be used to evaluate the batch for each of its critical variable factors (characteristics).]

"Many accomplished scientists in academia, government, and industry are working on these challenges, and there has been much success in recent years. But the fact remains that the pace of this development work has not kept up with the rapid advances in product discovery. The result is a technological disconnect between discovery and the product development process — the steps involved in turning new laboratory discoveries into treatments that are safe and effective."

While this commenter agrees that there is "a technological disconnect between discovery and the product development process," this commenter understands that this disconnect is mostly an artifact crafted by the industry for purposes that have been clearly discussed. [For example, in one case that this commenter is well aware of, a major vaccine firm deliberately chose to use non-standardized rodents ("to save money") for its batch release testing apparently because the inherent variability that using such contributed obscured the difference between "good" and "marginal" batches of their vaccines thereby allowing more batches to "meet specifications" and be released.]

"Although the FDA is just one participant in advancing development science, we have an important role to play. Because FDA's standards are often used to guide development programs, we need to make sure that our standard-setting process is informed by the best science, with the goal of promoting efficient development of safe and effective new medical treatments."

While this commenter agrees that the Agency needs “to make sure that our standard-setting process is informed by the best science, with the goal of promoting efficient development of safe and effective new medical treatments,” the reality is that the information furnished by pharmaceutical manufacturers in their applications not only fails to comply with the CGMP minimums in many areas but is also based on less-than-sound inspection plans that falsely equate the results from an insufficient number of non-representative samples to the properties of the batch or lot and use inappropriate sample specifications instead of valid batch acceptance criteria to determine the status of the untested majority of the units in the batch.

Given these realities, the Agency should severely penalize any firm found to be submitting applications that are knowingly deficient in the aforementioned areas and, until the firms can prove their full compliance with all of the explicit CGMP minimums in the development process for any batch administered to animals or humans, require the firms to submit not only all results data, including any “invalidated” values and the justification for their voiding, but also the written rationale that proves that the inspection plans and batch acceptance criteria used are scientifically sound and fully CGMP compliant.

“Because FDA is uniquely positioned to help identify the challenges to development, we need to work with the larger scientific community on developing solutions. Directed by Congress to promote and protect the public health, FDA is responsible for ensuring that safe and effective medical innovations are available to patients.² As part of its regulatory role, FDA must use available scientific knowledge to set product standards. During clinical testing, FDA scientists conduct ongoing reviews of emerging data on safety, efficacy, and product quality. Agency reviewers see the complete spectrum of successes and best practices during clinical trials, as well as the failures, slowdowns, barriers, and missed opportunities that occur during product development. When serious problems emerge in the development process or common problems continue to recur, FDA scientists attempt to address them by bringing them to the attention of the scientific community, or by conducting or collaborating on relevant research. As an example of such work, the Agency often makes guidance documents publicly available that summarize best practices in a development area and share FDA insights into specific issues or topics.

² See <http://www.fda.gov/opacom/hpview.html>.”

While this commenter agrees with the import of much that the Agency states here, this commenter notes that the firms often fail to provide **batch representative** “data on the safety, efficacy, and product quality.”

Since the preceding is the case, there is a **significant risk** (in some case, more than an 80 % risk) that the data reviewed does not reflect the true properties of the batch from which the samples tested were taken.

In addition, this commenter notes that there has recently been an increasing disconnect between the draft guidances published and the clear requirement minimums set forth in statutes, and the CGMP and, in some cases, other binding regulations, [Note: In the 1988 US Supreme Court case, **Berkovitz, Plaintiff v. United States (486 US 531, 100 L Ed 2d 531, 108 S Ct 1954)** the Supreme Court unanimously: **a)** overturned a US Appeals Court decision, **and b)** ruled that **FDA** administrators have **no** latitude with respect to interpreting any clearly written regulation. Specifically, the Court unanimously held that the Agency has no latitude to issue any documents that conflict with any clear regulation. Moreover, under the **Generic Drug Enforcement Act of 1992 (GDEA {United States Public Law (P.L.) 102-282 [106 Stat. 149 – 162]}**), any Agency personnel who issue such conflicting guidance may be liable under the general prohibition in **GDEA** that proscribe and criminalize the “subversion of the regulatory process.” Based on the preceding, the Agency needs to review any guidance document against the clear requirements of any regulation and void any and all guidance documents (draft and final) that plainly conflict with any clear regulation. This includes those recently issued draft guidances that bear on any aspect of the CGMP regulations for drugs and drug products (**21 CFR Parts 210 and 211**) (that also apply to biologic products) as well as the CGMP regulations for medical devices (**21 CFR Part 820**) and the recent final guidances issued for **21 CFR Part 11.**]

“Sponsors report that the availability of guidance documents has been shown to foster development and innovation in areas of therapeutic need, to improve the chances of initial success of a marketing application, and to shorten the time it takes to get safe and effective treatments to patients. But much more needs to be done. The product development problems we are seeing today can be addressed, in part, through an aggressive, collaborative effort to create a new generation of performance standards and predictive tools. The new tools will match and move forward new scientific innovations and will build on knowledge delivered by recent advances in science, such as bioinformatics, genomics, imaging technologies, and materials science.”

This commenter agrees with the Agency that “much more needs to be done.”

However, until: **a) batch representative** results are obtained, **b) valid batch acceptance criteria** are established, **and c) full CGMP compliance** is attained for the existing applications, performance standards, and predictive tools, it is premature to speak of creating a “a new generation of performance standards and predictive tools” that, *like the current ones*, will be neither **scientifically sound** nor **CGMP compliant**.

“FDA is planning an initiative that will identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path — safety assessment, evaluation of medical utility, and product industrialization. It is critical that we enlist all relevant stakeholders in this effort. We will work together to identify the most important challenges by creating a **Critical Path Opportunity List.**”

Without **scientifically sound batch-representative** data sets, the Agency's efforts in all three dimensions will be, at best, less than successful.

Unless the Agency requires those who submit their lists of "(1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits" to provide **scientifically sound** evidence supporting their lists, most of the lists that the Agency receives from the industry and those who benefit from its profitability will be nothing more than "wish lists" aimed at assisting the pharmaceutical in their apparent goal to "induce" an ever increasing percentage of the American population to taking an increasing number of their "treatment" drug products for the rest of their lives as well as, *where necessary*, other of their "treatment" products for the adverse side effects that their "treatment" drug products based on the often unsubstantiated grounds that such "may" improve the public's health, longevity, or reduce the public's risk of developing cancer or some other chronic disease state.

While such lists may lead to an increase in the number of applications submitted and the medical products approved, the increase in such *treatments* will not, in most cases, improve public health and, *because their increasing costs will limit access to only those that can afford the cost or those that the government, through taxation, directly pays the costs for*, actually decrease the healthcare provided to the general public by said "treatment" medical products.

At a minimum, the FDA should: **a)** focus such list initiatives on medical products that definitely **prevent** or **cure** medical problems, or that provide an order of magnitude improvement in the current treatment or reduction in their adverse side effects, **and b)** minimize the Agency's support for, and interest in, those new medical products that provide, *at best*, only a marginal improvement over the existing approved products for chronic palliative or condition mitigating treatments that do not **prevent** or **cure** the underlying "disease" state unless they are significantly less costly than the existing medical products for the same treatment.

To do this, the Agency should discourage "treatment" clinical trials against placebo unless there is no currently available effective "treatment" medical product and encourage (mandate) clinical trials where the current "most effective" approved "treatment" medical product is compared to the firms' putative "new treatment" with a requirement that the trial results show a significant advantage in either: **a)** treatment effect **or b)** side-effect reduction over the current "most effective" approved medical product. [**Note:** Had this been the Agency's position, Bayer's now withdrawn cholesterol-lowering statin drug "Baycol" would probably never have been approved and, *though Bayer would have lost some development money*, the injuries and deaths caused by Baycol would have been avoided. Moreover, Bayer would have avoided having to pay out millions of dollars to settle the injury and wrongful death claims arising from this medical product. There are other recently withdrawn or

“re-labeled to restrict use” medical products for which the adverse public-health effect costs seemingly do not support the Agency’s current position of continuing to approve medical products that are fundamentally only more effective than a placebo as long as their health risks to those who are prescribed said medical products are not “obviously lethal.”]

“Concurrently, FDA will refocus its internal efforts to ensure that we are working on the most important problems and intensify our support of key projects. Through scientific research focused on these challenges, we can improve the process for getting new and better treatments to patients. Directing research not only to new medical breakthroughs, but also to breakthrough tools for developing new treatments, is an essential step in providing patients with more timely, affordable, and predictable access to new therapies. We are confident that, with effective collaboration among government, academia, and the private sector, these goals can be achieved.”

This commenter finds it odd that the Agency is “refocusing its internal efforts” to improving “the process for getting new and better treatments to patients” rather than focusing on finding medical products that are either preventive or curative.

It would certainly benefit the public health more if the government focused its efforts on preventions and cures, and left “treatments” to the self-serving interests of the pharmaceutical industry to continue to develop “better” (certainly, at least, more profitable) palliative or mitigating treatments rather than preventive or curative medical products.

After all, once approved, direct-to-the-consumer advertising, marketing and the “free market” rather than public-health benefit seems to dictate which of the competing treatments for a given medical condition (e.g., “acid reflux”) or putative medical health risk (e.g., the risk of developing cancer, “type 2” diabetes, coronary heart disease) becomes dominant in the healthcare marketplace.

The preceding seems to be the case even in instances where firms knowingly engage in violative off-label promotion of an approved drug to markedly increase its profitability (market) since, *based on the most recent case*, the “negotiated” penalties imposed when such schemes are exposed are only a small fraction of the profit made and, *though the firm was forced to stop its off-label promotion*, many of the doctors “conditioned” to prescribe said medical product will continue to do so and thereby ensure a continuing inflated revenue stream for said manufacturer into the foreseeable future.

Obviously, *as long as the potential for profit far outweighs the cost of the violative marketing practices used*, profit-driven pharmaceutical firms will have little, or no, incentive to not engage in such schemes.

“FDA is planning an initiative that will identify and prioritize the most pressing development problems and ... the greatest opportunities for rapid improvement”

Based on the Agency's rhetoric, having decided that the problem is "product development" and wishing to help the pharmaceutical industry even more than it is currently, the FDA is seeking to have the industry tell the Agency what the industry's "greatest opportunities for rapid improvement" wish list is.

This is the obviously case because an announced (published in Federal Register) initiative with an initial "90 day" closing date presents little risk that the general public or academics outside of those who are involved with the pharmaceutical industry will initially comment.

"Introduction

The mission of the U.S. Food and Drug Administration (FDA) is, in part, to protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines to improve their health."

This commenter fully agrees with all that is stated here but notes that some of the activities that the Agency is currently engaged in do not seem to be aligned with what is stated.

"In keeping with its mission, FDA is issuing this report to address the growing crisis in moving basic discoveries to the market where they can be made available to patients. The report evaluates how the crisis came about and offers a way forward. It highlights examples of Agency efforts that have improved the critical path and discusses opportunities for future efforts. Finally, the report calls for a joint effort of industry, academia, and the FDA to identify key problems and develop targeted solutions."

This commenter finds it is less than responsible to cast a putative "submission-rate slowdown problem" over a short period of time (the last decade) as a "growing crisis" – especially in light of the information presented in an article, discussed in the introduction section, entitled "The Real Capacity Crisis" that indicates that there will soon be a marked upturn in both "NME" and "BLA" submissions.

"Figure 1: 10-year Trend in Biomedical Spending"

This figure actually shows more than a non-inflation-corrected doubling in spending that, after correction for inflation, is:

- a) Less than a doubling,
- b) Less than the increase in the prices justified by the industry based "increased development costs," **and**
- c) Significantly less than the revenue increases realized by the manufacturers of said medical products.

“Figure 2: 10-year Trends in Major Drug and Biological Product Submissions to the FDA”

1. For “Major Drugs,” this figure actually shows an increase in “Major Drug” submissions from 1993 through 1995 followed by a gradual return to about the same level as in 1993 in 2003 – far from a crisis.
2. For “Biological Products,” this figure does show a decrease from 1993 to 2003, but, *as the previously discussed article in Pharmaceutical Engineering clearly indicates*, this is a transient phenomenon.
3. However, lacking the figures for the number of approvals granted and the INDs filed, the raw submission numbers are not valid indicators of a “problem” in a decline in the rate of availability of safe and effective treatments nor of a “disconnect” between discovery and new medical products being submitted. [Note: History has shown: **a**) many of the initial “scientific discoveries” and “medical breakthroughs” have not proven to be applicable to humans **and b**) that true discovery and breakthrough is a discontinuous process characterized by a torrent of productive activity after the initial event that tapers off over time until the next such true event triggers the next torrent of productive activity. Given these historical realities, the data plotted in **Figure 2** certainly does not support the Agency’s “downturn problem” for “Major Drugs” nor an overall “growing crisis” or, for that matter, *without showing the data for INDs, approvals and licenses*, any “crisis” in the availability of cures and truly better treatments to the public in general. All that the data shows is that the “medical products” industry is currently between major “breakthrough” events.]

“Innovation or Stagnation?”

Challenge and Opportunity on the Critical Path to New Medical Products

The sequencing of the human genome four years ago raised widespread hope for a new era in the prevention and treatment of disease created by the ongoing investment in biomedical research (Figure 1). But that new era has not yet arrived. Instead, 2000 marked the start of a slowdown in new³ drug and biologic submissions to regulatory agencies worldwide (Figure 2). The submission of innovative medical device applications has also slowed recently.⁴ This means fewer new products can be approved and made available to patients. At a time when basic biomedical knowledge is increasing exponentially, the gap between bench discovery and bedside application appears to be expanding. There is great concern about the ability to bring the hoped-for outcomes of basic research advances — much awaited new treatments — to patients. There is concern that hoped-for advances in medicine and new treatments for diseases may never materialize.

³ For purposes of this document the terms novel or new refer to applications for medical products of a type that have never before been submitted to the Agency (i.e., new molecular entity - NME).

⁴ See <http://www.fda.gov/cdrh/consumer/mda/index.html>.”

This commenter finds that, as discussed for the data in the figures themselves, the Agency's statements concerning **Figures 1** and **2** is mostly rhetoric and, in the case of **Figure 2**, rhetoric concerning the worldwide state of affairs that is not supported by the information provided in said figure.

Since many of the currently available medical products and the submissions for new medical products are current-therapy-related medical products, one should not, as this text does, attempt to "equate" or "link" the number of medical products available, *or potentially available*, to the state of, *or the quality of*, the available patient health care.

In general, the availability of more medical products has a better correlation with the increase in healthcare costs to the public than the improvement in healthcare available to the general public.

Finally, this commenter notes that the FDA has failed to even mention its self-serving reason for wanting more submissions, namely that the Agency receives significant revenue from each such submission – the more submissions, the more review funds.

At a minimum, the Agency needs to forthrightly address this conflict that, *based on the baseless "healthcare crisis" rhetoric used*, seems to, *at a minimum*, have strongly influenced the Agency's finding of this "problem" as well as the casting of the "problem found" in terms of a slowdown in "submissions" and a "crisis" rather than presenting the problem in terms of the number and rate of medical products "accepted."

As for the Agency's voiced "concern" that "hoped-for advances in medicine and new treatments for diseases may never materialize," this commenter can only note that history does not support the Agency's concern:

- a) In spite of the pharmaceutical and medical industries' resistance to implementing the medical cure for simple ulcers (from the 1980s until the present) and its less-than-most-effective diagnosis and therapy regimen, a fairly effective ulcer *cure* is available to the public today for such ulcers
- b) In spite of the pharmaceutical industry's refusal to push the vaccine for HPV-16 and HPV-18 (a certain preventive measure for these cervical-cancer-associated sexually transmitted diseases that, *based on the 100% effective clinical trial*, would surely reduce the incidence of virus-induced cervical cancer in all protected by this vaccine), hopefully, in the not-too-distant future, that vaccine will be prescribed for both sexes at around their 10th birthday with "10-year boosters," and cervical cancer rates will be reduced even though that reduction in cervical cancer rates will cost both the pharmaceutical and medical industries a significant "treatment" revenue stream.
- c) Hopefully, *with the ready availability of a quick prenatal screening test for the sexually and maternally transmitted Hepatitis B*, the practice of vaccinating all newborns against Hepatitis B will be stopped and only

those babies at risk will be vaccinated thus reducing the number of newborns damaged by the adverse reactions to this vaccine that occur in a small percentage of the babies currently unnecessarily vaccinated – even though this too will reduce the “Hepatitis B” vaccine revenues that the pharmaceutical industry now receives.

This commenter only wishes that the Agency was half as concerned about the preceding “delays” of cures, “unnecessary” treatments, and other similar realities (dangerous medical products that the industry was allowed to market until their adverse effects forced them off of the market) as it is about the current “apparent” downturn in the number of submissions that, *based on history and recently published articles*, is a transient event.

“Current costs of bringing a new medicine to market, estimated by some to be as high as \$0.8 to 1.7 billion,⁵ are a major barrier to investment in innovative, higher risk drugs or in therapies for uncommon diseases or diseases that predominantly afflict the poor. Product development in areas crucial to public health goals, such as antibiotics, has slowed significantly during the past decade. Inventors of candidate artificial organs, bioengineered tissues, and other novel devices face serious challenges and uncertainties. A viable path for developing many preventive therapies (e.g., some types of cancer chemoprevention) has not been elucidated.

⁵ Tufts Center for the Study of Drug Development, *Backgrounder: How New Drugs Move Through the Development and Approval Process*, Boston: November 2001; and Gilbert J, P Henske, and A Singh, ‘Rebuilding Big Pharma's Business Model,’ *In Vivo*, the Business & Medicine Report, Windhover Information, Vol. 21, No. 10, November 2003.”

Though this commenter cannot disagree with the text, he wonders what is the purpose behind the statements since no supporting documentation for the validity of the information furnished is provided and the statements made do not directly bear on the Agency’s putative “submission-decline problem”/“crisis.”

Further, *based on this commenter’s direct and indirect knowledge of industry practices*, these costs are often deliberately inflated especially when a foreign-based company charges its US operations for such costs and thereby effectively shield some of their profit from the little taxes owed while, to the extent such are available, maximizing their research credits – an effective double-win tax avoidance tactic – of course US-based firms can also inflate their costs and similarly enhance any “research” tax credit.

Since there is no way to independently assess the costs and since, *as far as this commenter can ascertain*, said costs, *though artificially inflated*, are growing less rapidly than the firms’ revenue stream and profit, it would seem that these are just a cost of doing business that does, *as the Agency notes*, lead to the emphasis of medical “treatment” products that have the highest potential for profit, at the expense of “preventive” and “curative” therapies.

However, *given the obvious proven greed-driven imperatives of today's pharmaceutical and healthcare industries*, this would be the case regardless of whether the costs increase or decrease just as the pharmaceutical industry chooses to spend increasing larger sums on marketing and direct-to-the-consumer advertising while decreasing their expenditures in the product-quality area even though their manufacturing operations, *as the recent consent decrees, fines, and lawsuits by whistleblowers clearly demonstrate*, do not meet the CGMP **minimums** required for the legal production and sale of said medical products..

“Figure 3: Investment Escalation per Successful Compound”

This figure provides an example of an apparent “average” increase in the costs for the period 2000-2003 over the period 1995-2000 apparently without correcting the sums stated for inflation.

Since the comparison is between unequal periods and the effect of inflation was not factored in, the apparent 55 % increase from 1.1 to 1.7 billion dollars is probably less than half of that in inflation-corrected dollars and the periods were probably chosen to maximize the increase (for a valid comparison, the period 2000-2003 costs should have been compared to the period 1997-2000 costs).

In the figure, the “Launch” costs seem to have remained the “same” with significant reported increases in the “Discovery,” “Phase II,” and “Phase III/Application” areas but not in the “Preclinical” and “Phase I” areas – moreover, the figure conveniently leaves out the Post-approval monitoring costs.

“Figure 4: The Critical Path for Medical Product Development”

This figure delineates the phases as “Basic Research,” “Prototype Design or Discovery,” “Preclinical Development,” “Clinical Development,” and “FDA Filing/Approval & Launch Preparation” with a “milestone” labeled “Market Application” towards the end of the “Clinical Development” phase and “Approval” at the end of the “FDA Filing/Approval & Launch Preparation” phase.

In addition, the figure depict the “Critical Path” as a bar-delimited line which the Agency shows begins somewhere in the “Prototype Design or Discovery” phase and ends after “Approval” is obtained – a distinctly drug-product view.

However, *since the Agency has included the decline in research in certain areas as one aspect of the current “problem,”* it is obvious that the **true** “Critical Path” begins in the “Basis Research” area and, since, *in most cases, Post-approval Monitoring is required*, properly ends only when the requisite intensified *Post-approval Monitoring* establishes that the medical

product actually does have an adequate patient safety and efficacy profile to justify its being left on the market without a significant label restriction upgrade or revision.

“Recent basic science achievements promise significant payoffs in human health, but these potential benefits are threatened by low productivity — measured by the high costs and high risks of failure in the current development processes and the declining number of successful products reaching patients. Often, developers are forced to rely on the tools of the last century to evaluate this century’s advances. And the situation does not appear to be improving. Recent data suggest that the investment required to launch a new drug has risen 55 percent during the last five years (Figure 3). Pharmaceutical, biotechnology, and medical device productivity appears to be declining at the same time that the costs to develop a small number of treatments are rising.

Based on the rhetoric and the misstatement concerning the implications of **Figure 3**, it seems to this commenter that this text was drafted more by an industry marketer than a science-based regulatory body.

For example the denigrated “tools of the last century” are, in many cases, less than 5-years old, not as the implied 100-years old that the use of the word “century” connotes – since most of the tools currently being used are, *in their current form*, less than a decade old, that is the contextual reference frame, the decade, that should have been used had the writers been interested in accurately characterizing the current situation.

Moreover, statements containing words such as “appear” should obviously be ignored because no body of substantiating evidence encompassing the period from 1904 through 2004 is being offered, or referenced, as it should be if one truly wishes to see what the historical realities, patterns and trends are rather than, *as these authors seemingly have done*, ignoring the patterns of history and focusing on what the current non-normalized cost and submissions data are without even bothering to look at the effective number of FDA-accepted products that are still on the market without a significant restriction in their label for more than 5 years or, *for products on the market for at least a year but less than 5 years past FDA-acceptance*, that are currently projected to: **a) remain on the market and/or b) not require increased usage restrictions on their labeling for the foreseeable future.**

In addition, the NME and BLA data do not seem to be corrected by eliminating the “similar” or “related new medical products that address the same conditions as a currently approved medical product but do not provide any significant real therapeutic advantage over said approved medical product.

Finally, the issue of approved products that have been removed from the market because their true risks have been shown to far outweigh their supposed benefits (e.g., FEN/PHEN, the Lyme vaccines, Baycol, Resulin,

etc.) and the damage such products have inflicted on the public are not even mentioned much less addressed as an issue.

“If biomedical science is to deliver on its promise, scientific creativity and effort must also focus on improving the medical product development process itself, with the explicit goal of robust development pathways that are efficient and predictable and result in products that are safe, effective, and available to patients. We must modernize the critical development path that leads from scientific discovery to the patient (Figure 4).”

While this commenter finds the text interesting, it is not persuasive because it ignores the reality that the industry has been and is knowingly engaged in operation in a manner that: **a)** routinely does not comply with the CGMP minimums for medical products **and b)** markets batches of drugs that have the results data which provide less than 20 % confidence that, at release, each unit in the batch meets the expected specification minimums established for said medical products – much less their non-existent CGMP compliant batch release specifications.

Rather than “modernizing” the path, the Agency should be focusing its efforts on assuring that the manufacturers follow the “true” critical development path in a manner that full compliance to all CGMP **minimums** is maintained from the time the putative medical product is first administered to humans in the “Preclinical” phase onwards in a manner that guarantees that:

- a. The critical characteristics (physical and chemical) of all inputs are rigorously controlled in a manner that fully complies with the CGMP minimums appertaining thereto,
- b. All manufacturing process steps are adequately controlled and monitored in a CGMP-compliant manner,
- c. The in-process materials from each *significant* manufacturing phase are *representatively inspected* against *scientifically sound specifications appropriate* to each such material,
- d. All evaluation results at release are obtained on sufficient representative samples to meet the number requirements for a 95%, or higher, confidence level, and
- e. Each batch released meets each appropriate specification and appropriate statistical quality control criteria as one of the conditions for its release (and the USP’s specifications are neither scientifically sound nor appropriate for batch acceptance for release).

Having personally witnessed both late-stage and post-approval product failures whose root causes were the failure too develop said products in full compliance with the CGMP minimums established for said products, this commenter knows that, *until the medical products industry meets the current product development strictures and submits applications in which all samples are representative of the batch and/or process that carry with them a 95% or higher confidence level in their ability to be predictive of the*

untested population, much of the non-productive effort in the development process that the medical process industry currently uses will continue unabated and/or, *in some instances*, may actually increase.

“Often, developers are forced to use the tools of the last century to evaluate this century’s Advances”

As stated previously, the denigrated “tools of the last century” are, *in many cases*, no more than 5-years old and not, *as the use of the word “century” implies*, 100-years old – since most of the tools currently being used are, *in their current form*, less than a decade old, this “decade old” context is reference frame that should have been used had the writer been interested in presenting a less biased picture of the current reality.

“In response to the widening gap between basic biomedical knowledge and clinical application, governments and the academic community have undertaken a range of initiatives. After decades of investment in basic biomedical research, the focus is widening to include translational research — multidisciplinary scientific efforts directed at “accelerating therapy development” (i.e., moving basic discoveries into the clinic more efficiently).⁶ Notable are:

- National Institutes of Health (NIH) Roadmap, announced in September 2003. This is a series of initiatives intended to “speed the movement of research discoveries from the bench to the bed side”⁷
- National Cancer Institute's (NCI) Specialized Programs of Research Excellence (SPOREs)⁸
- MdBIO, a private nonprofit corporation that supports the growth of bioscience in Maryland⁹
- The European Organization for the Treatment of Cancer (EORTC) is committed to making translational research a part of all cancer clinical trials¹⁰
- The British government announced the National Translational Cancer Research Network to facilitate and enhance translational research in the United Kingdom¹¹

⁶ Finkelstein R, T Miller, and R Baughman, ‘The Challenge of Translational Research—A Perspective from the NINDS,’ *nature neuroscience supplement*, Vol. 5, November 2002.

⁷ See nihroadmap.nih.gov/overview.asp.

⁸ See http://spores.nci.nih.gov/applicants/guidelines/guidelines_full.html#1b.

⁹ See www.mdbio.org.

¹⁰ Eggermont A and H Newell, ‘Translational Research in Clinical Trials: The Only Way Forward,’ *European Journal of Cancer*, Elsevier Science, 37 (2001). EORTC also set up in October 2002 the Translational Research Advisory Committee to support and provide expert advice on translational research projects conducted within EORTC.

¹¹ Rowett, L, ‘U.K. Initiative to Boost Translational Research,’ *Journal of the National Cancer Institute*, Vol. 94, No. 10, May 15, 2002.”

Having worked for a firm that had “pilot plant,” “analytical R&D,” and “technology transfer” groups in the 1970’s that were fully engaged in what is now labeled “translational research — multidisciplinary scientific efforts directed at accelerating therapy development,” this commenter knows that, *while much of that effort has been misdirected and/or based on less than sound science*, the industry has been engaged in such activities since at least the 1970’s.

Given the proliferation of such initiatives in government and quasi-governmental agencies, it seems obvious that, *having successfully transferred the costs for much of the basic research from themselves to the government*, the industry, *with the Agency’s assistance*, is now seeking to transfer the costs of this “translational research” from themselves to the government – an effort to reduce their costs and further improve their profitability at the public’s expense – the medical products industry is no longer content to profit from government funded discoveries (e.g., AZT), they now want the government to also bear the initial development costs of the drugs discovered..

As evidence of this reality, this commenter offers the recent “**60 Minutes**” segment in which an industry spokesman stated that the government should, *in the near future*, pay the industry to develop new antibiotics if the government wanted such “low profit” drugs developed by the industry.

“Figure 5: Research Support for Product Development”

This figure shows the steps that the Agency places within the “Translational Research” phase – the figures starts this phase at the end of the “Basic Research” phase and ends it somewhere in the “Clinical Development” phase.

In addition, the figure depicts a “Critical Path Research” phase that starts at the end of the “Prototype Design or Discovery” phase and ends in the “FDA Filing/Approval & Launch Preparation” phase.

“Although necessary for product development, these translational research efforts will not yield the hoped-for results without an analogous focus on downstream development concerns. As one group has observed, ‘Massive investments in one part of the network are likely to be at least partly wasted unless the other links are strengthened as well.’¹² A third type of scientific research is urgently needed, one that is complementary to basic and translational research, but focuses on providing new tools and concepts for the medical product development process — the steps that must be taken to get from selection of a laboratory prototype to delivery of an effective treatment to patients. We call this highly targeted and pragmatic research critical path research because it directly supports the critical path for product development success (Figure 5).

¹² Baumann M, SM Bentzen, W Doerr, MC Joiner, M Saunders, et al., ‘The Translational Research Chain: Is It Delivering the Goods?’, *Int. J. Radiation Oncology Biol.Phys.*, Vol. 49, No. 2, 2001, Elsevier Science.”

Not content to have the government underwrite an increasing share of the “Translational Research” phase, the Agency is also proposing that the government needs to underwrite a “Critical Path Research” phase to complete the process.

Instead of adding “Critical Path Research” phase, the Agency would be better served if it simply required manufacturers to fully comply with all of the applicable CGMP **minimums** that, in general, these medical product manufacturers seem to be, or are, knowingly ignoring.

Again, *as this commenter has previously stated*, the Agency should be focusing its efforts on assuring that the manufacturers follow the “true” critical development path in a manner that full compliance to all CGMP **minimums** is maintained before the time the putative medical product is first administered to humans in the “Preclinical” phase onwards, *including in the Agency’s “Critical Path Research” phase*, in a manner that guarantees that:

- a. The critical characteristics of all process inputs are rigorously controlled in a manner that fully complies with the CGMP **minimums** appertaining thereto,
- b. All manufacturing process steps are adequately controlled and monitored in a CGMP-compliant manner,
- c. The in-process materials from each significant manufacturing phase are *representatively inspected* against *scientifically sound and appropriate specifications* for each such material,
- d. All results are obtained on sufficient *representative samples* to meet the number requirements for a valid 95%-, or higher, confidence-level prediction of the critical characteristics of the untested majority of the units in batch or, for medical devices, sufficient measurements are taken to ensure that each device fully meets its targeted safety, efficacy, and other quality-related specifications, and
- e. Each batch released meets each *appropriate specification* and *appropriate statistical quality control criteria* as one of the conditions for its release (and, *for drugs, including biologicals*, the USP’s specifications are neither *scientifically sound* nor *appropriate* for *batch acceptance* for release [as the USP notes in its **General Notices**]).

“Massive investments in one part of the network are likely to be at least partly wasted unless the other links are strengthened as well”

While this commenter agrees with this statement, this commenter understands that what is first required is for the medical products industry to

operate in full compliance with all of the applicable CGMP *minimums* – an obvious deficiency that has been documented many times in the recent years and one that pervades the medical products industry especially in the medical products' development arena.

“Negotiating the Critical Path

To get medical advances to patients, product developers must successfully progress along a multidimensional critical path that leads from discovery or design concept to commercial marketing.”

This commenter agrees with the Agency's statement here.

“Currently, a striking feature of this path is the difficulty, at any point, of predicting ultimate success with a novel candidate. For example, a new medicinal compound entering Phase 1 testing, often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market. This reflects a worsening outlook from the historical success rate of about 14 percent.¹³ In other words, a drug entering Phase 1 trials in 2000 was not more likely to reach the market than one entering Phase 1 trials in 1985.¹⁴ Recent biomedical research breakthroughs have not improved the ability to identify successful candidates.”

¹³ Gilbert J, P Henske, and A Singh, ‘Rebuilding Big Pharma's Business Model,’ In Vivo, the Business & Medicine Report, Windhover Information, Vol. 21, No. 10, November 2003.

¹⁴ Lloyd I, ‘New Technologies, Products in Development, and Attrition Rates: R&D Revolution Still Around the Corner,’ in PARAXEL'S Pharmaceutical R&D Statistical Sourcebook 2002/2003.

Since the Agency provides only secondhand estimates of what reality may be and basic biomedical research have not been directed toward improving said ability, this commenter must disregard most of the rhetoric presented in this paragraph.

“The main causes of failure in the clinic include safety problems and lack of effectiveness: inability to predict these failures before human testing or early in clinical trials dramatically escalates costs. For example, for a pharmaceutical, a 10-percent improvement in predicting failures before clinical trials could save \$100 million in development costs per drug.¹⁵ In the case of medical devices, current capacity for technological innovation has outstripped the ability to assess performance in patients, resulting in prolonged delays between design and use. For very innovative and unproven technologies, the probability of an individual product's success is highly uncertain, and risks are perceived as extremely high. Whole fields may stagnate as a result of the failure of early products. The goal of critical path research is to develop new, publicly available scientific and technical tools — including assays, standards, computer modeling techniques, biomarkers, and clinical trial endpoints — that make the development process

itself more efficient and effective and more likely to result in safe products that benefit patients. Such tools will make it easier to identify earlier in the process those products that do not hold promise, thus reducing time and resource investments, and facilitating the process for development of medical products that hold the most promise for patients.

¹⁵ Boston Consulting Group, ‘A Revolution in R&D: How Genomics and Genetics Will Affect Drug Development Costs and Times,’ in PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2002/2003.”

Like Henney Penney, the Agency presents an unsubstantiated “sky is falling” scenario that is based on the Agency’s review of the unverified secondhand reporting of information provided by an industry, the medical products industry, that has repeatedly been found to be less than truthful in its declarations.

While the Agency’s stated “critical path research” goal of developing “new, publicly available scientific and technical tools — including assays, standards, computer modeling techniques, biomarkers, and clinical trial endpoints — that make the development process itself more efficient and effective and more likely to result in safe products that benefit patients” is laudable, it ignores the reality that most firms, *having developed such “tools,”* withhold said “tools” from the public until they no longer provide that firm with a commercial advantage over that firm’s competitors. [Note: Having worked for a major firm and discovered several such “tools,” *including one that some 25 years later still remains unpublished,* and having been involved in developing methods that were intended only for in-house use as well as others that were intended for and included in various firms’ submissions, this commenter knows that some of these “needed tools” exist and are already being used, but, *because of the competitive advantage they provide,* said “tools” are zealously guarded by the firms that have developed and routinely use them.]

Based on the preceding realities, this commenter knows that the Agency’s laudable goal is neither realistic nor attainable.

As it has for the past hundred years, most of the publicly available “tools” of the types envisioned by the Agency will remain a decade or more behind the actual state-of-the-art “tools” developed and used by the cutting edge firms in the medical products industry regardless of the effort expended by governmental agencies to “improve” the “public” availability of such “tools” unless the FDA intends to breach the confidentiality that the Agency is required by law to maintain.

“The goal of critical path research is to develop new ... scientific and technical tools ... that make the development process itself more efficient and effective”

While this may be laudable, this goal is not an objective that the FDA, *charged with protecting the public health,* should be undertaking until and unless the Agency has:

- Effectively addressed its primary “public health protection” mandates,
- Met its statutory biannual inspection mandates with full inspections of all systems, **and**
- Found that the overwhelming majority of firms are operating in an ethical, transparent manner that fully meets, or exceeds, all of the clear CGMP requirement **minimums** as required by law.

“Scientific and Technical Dimensions Along the Critical Path

Whether working with devices, drugs, or biologicals — medical product developers must negotiate three crucial scientific/technical dimensions on the critical path from scientific innovation to commercial product (Table 1 on the following page). These three dimensions are interdependent, and in none is success assured. The vast majority of development costs are attributable to these three dimensions.”

This commenter agrees with the Agency here.

“Developers must manage the interplay between each dimension from the earliest phases of development. For example, the first dimension — **ensuring product safety** — is crucial to consider when designing a drug molecule, choosing production cell lines or reference strains for biological production, or selecting biomaterials for an implanted medical device (Figure 6 on the following page). The traditional tools used to assess product safety — animal toxicology and outcomes from human studies — have changed little over many decades and have largely not benefited from recent gains in scientific knowledge. The inability to better assess and predict product safety leads to failures during clinical development and, occasionally, after marketing.”

While this commenter agrees with much of what the Agency states, this commenter does not agree that the “tools used to assess product” have:

- a. “changed little over many decades” **or**
- b. “not benefited from recent gains in scientific knowledge.”

Since many of the advances are held in strict confidence by the firms who have developed and use them, *because of the commercial advantage they provide said firms*, much of the real scientific progress is not even revealed to the FDA much less the “public.”

Moreover, in many cases, the real product-safety-related reason for clinical and post-marketing safety problems and failures is more often the reality that the firms in question not only ignored one or more of the “warning signals” that the outcomes from “animal toxicology and outcomes from human studies” furnished but also failed to disclose the adverse study (e.g., Accutane) or, through the misuse of statistical analysis, deliberately obscured the adverse indicator as much as possible.

Further many of the problems were noted by an Agency committee or application reviewer but were considered an acceptable risk by the Agency

who approved the medical product in spite of the warning flags in the safety data (e.g., Resulin).

Based on the preceding, the Agency needs to strengthen its application review process to:

- Ensure that Agency personnel, and not the submitter, evaluate the raw safety results from all studies, **and**
- Increase the weight given to any safety-related adverse finding.

Were the Agency to uniformly do this, the industry would adjust its filtering process accordingly and weed out more of those new medical products, which have some safety concerns (by lowering their safety-issues-risk threshold).

“The second dimension, **demonstrating the medical utility** of a new product — showing that it will actually benefit people — is the source of innumerable failures late in product development. Better tools are needed to identify successful products and eliminate impending failures more efficiently and earlier in the development process. This will protect subjects, improve return on R&D investment, and bring needed treatments to patients sooner.”

While text is correct, this commenter again notes that, *by not operating in a fully CGMP-compliant manner that generate highly uniform and reproducible products, and takes and tests a sufficient number of batch representative samples to ensure at least a 95% confidence level in the findings from any study*, the medical products industry has deliberately chosen to operate in the high-risk, low confidence mode described by the Agency when it comes to “**demonstrating the medical utility** of a new product.”

After all, operating in the CGMP-compliant manner outlined would raise the costs of the required studies for all candidates – something that the industry obviously does not want to do.

Since the less costly smaller number of tests carry with them a lower level of confidence (in some cases, less than 20 %) that the outcomes observed are valid and reproducible, it is little wonder that pursuing such experimental designs leads to “failures late in product development.”

Based on the reality of the preceding, this commenter knows that CGMP-compliant, 95% (or higher) confident manufacturing processes coupled with similarly predictive experimental studies, *and not better tools*, would do more to reduce the number of “failures late in product development.”

After all, *though the tools have improved over the past 25 plus years that this commenter has been involved in the discovery, development, manufacturing, and inspection of bioactive compounds*, the industry’s stated overall success rate has not increased significantly – and, *if the Agency statements are accepted as valid*, it has even apparently decreased.

If the lack of better tools were real problem, then the success rate should have increased slightly over that time period because the tools available for use and used most certainly have improved significantly – but this has not been the case.

This commenter again suggests that the Agency would better serve the public if it were, *during the development process*, to require both: **a)** full CGMP compliance **and b)** valid 95%-confidence level (or a higher level) outcome-predictive experimentation in studies from the Pre-clinical phase onwards.

“A number of authors have raised the concern that the current drug discovery process, based as it is on in vitro screening techniques and animal models of (often) poorly understood clinical relevance, is fundamentally unable to identify candidates with a high probability of effectiveness.^{16,17} The current scientific understanding of both physiology and pathophysiologic processes is of necessity reductionistic (e.g., is knowledge at the gene, gene expression or pathway level) and does not constitute knowledge at the level of the systems biology of the cell, organ, or whole organism, and certainly does not reach a systems understanding of the pathophysiology of particular diseases. Reaching a more systemic and dynamic understanding of human disease will require major additional scientific efforts as well as significant advances in bioinformatics. Nevertheless, progress in discovery will continue,¹⁸ and as candidates emerge, the best tools available should be used for their evaluation. This will require strengthening and rebuilding the relevant disciplines (e.g., physiology, pharmacology, clinical pharmacology) and working to identify ways to bridge between the laboratory and the whole organism and correlate early markers of safety and benefit with actual outcomes in patients. In addition, it is likely that more interest will develop in earlier "proof-of-concept" trials that seek to confirm activity in humans before a commitment to full-scale development is made. The FDA is working to facilitate such studies.

¹⁶ Duyk J, ‘Attrition and Translation,’ *Science*, Vol. 302, October 24, 2003.

¹⁷ Horrobin DF, ‘Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?,’ *Nature Reviews Drug Discovery*, Vol. 2, No. 2, February 2003.

¹⁸ Glassman RH, and AY Sun, ‘Biotechnology: Identifying Advances from the Hype,’ *Nature Reviews Drug Discovery*, Vol. 3, No. 2, February 2004.”

While this commenter does not disagree with the preceding text, research in these areas should be left to the medical products industry and the current government funded academic research.

Because it is ill equipped to formulate much less carry out such research or, based on its performance, scientifically evaluate the results obtained, the FDA should not become involved in what is basic research outside of its mandate to protect the public health.

This is the case because the Agency’s plate is already overflowing with many mandated activities whose statutory requirements and expectations the Agency currently is not even attempting to meet.

“Table 1: Three Dimensions of the Critical Path

Dimension	Definition	Example of Activities
Assessing Safety	Show that the product is adequately safe for each stage of development	<ul style="list-style-type: none"> • Preclinical: Show that the product is safe for early human testing Eliminate products with safety problems early • Clinical: Show that the product is safe enough for commercial distribution
Demonstrating Medical Utility	Show that the product benefits people	<ul style="list-style-type: none"> • Preclinical: Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness • Clinical: Show the effectiveness in people
Industrialization	Go from lab concept or prototype to a manufacturable product	<ul style="list-style-type: none"> • Design a high quality product <ul style="list-style-type: none"> – Physical design – Characterization – Specifications • Develop mass production capacity <ul style="list-style-type: none"> – Manufacturing scale-up – Quality control

This table refers to scientific and technical dimensions. Other business dimensions (e.g., obtaining capital, intellectual property considerations, marketing and distribution arrangements) are not within the scope of this table.”

While most of “Table 1” adequately conveys the minimum requirements, the definition of the “Industrialization” is both: **a)** too simplistic **and b)** at odds with what is required.

Properly, the simple definition of “Industrialization” should be:

“Go from lab concept or prototype to a *reliably* manufacturable product *that meets or exceeds all of the applicable CGMP minimums*”

because most of the problems in both: **a)** the development of a new medical process, **and b)** the product produced by it, can be traced to a failure to reliably manufacture product that meets or exceeds all of the applicable CGMP *minimums*.

Though “obvious,” this commenter would also suggest modifying the definition of “Assessing Safety” to read:

“Show that the product is adequately safe for each stage of development *at an initial statistical confidence level of not less than 99%*”;

and the definition of “**Demonstrating Medical Utility**” to read:

“Show that the product benefits people *at a statistical confidence level of not less than 95%*.”

With these modifications, this commenter knows that many of the late clinical failures and the post-release safety, efficacy and manufacturing problems would be greatly reduced even when the related “tools” do not incorporate the best available scientific and technical advances.

“Figure 6: Working in three Dimensions on the Critical Path”

First, this commenter generally agrees with this figure’s caption, “Figure 6 is a highly generalized description of activities that must be successfully completed at different points and in different dimensions along the critical path. Many of these activities are highly complex – whole industries are devoted to supporting them. Not all the described activities are performed for every product, and many activities have been omitted for the sake of simplicity.”

However, this commenter would place the beginning of the “**Safety**” dimension in the “Basic Research” phase and continue it into the “Post-launch” phase.

Similarly, the start of both the “**Medical Utility**” and “**Industrialization**” dimensions should be in the “Basic Research” phase, and both should and do, *unlike depicted in the figure*, extend into the “Post-launch” phase with “**Industrialization**” being an obviously life-long journey predicated upon the statutory requirement to maintain the process and product within the established *minimums* for the ever evolving envelope of what is truly “current minimum good manufacturing practice” (CGMP).

Provided this figure is revised to reflect the realities outlined, the view in said figure would be aligned with the clear binding CGMP regulations appertaining thereto.

“The final dimension on the critical path can be described as the **industrialization process** — turning a laboratory concept into a consistent and well-characterized medical product that can be mass produced. The challenges involved in successful industrialization are complex, though highly underrated in the scientific community. Problems in physical design, characterization, manufacturing scale up and quality control routinely derail or delay development programs and keep needed treatments from patients. These problems are often rate-limiting for new technologies, which are frequently more complex than traditional products and lack standard assessment tools.’

Again, this commenter cannot agree with the Agency’s position and statements.

In the biotechnology area, *based on his knowledge and understanding of the true barriers*, this commenter agrees with the closing remarks of Jeff Odom in his article, “The Real Capacity Crisis” (*Pharmaceutical Engineering*, **24(3)**, page 116 [May/June 2004]), “The looming capacity crisis is not in stainless steel or in production facilities. It is the crisis of human resources. And it is a crisis that we cannot ignore.”

Moreover, In the biological, traditional drugs and device areas, this commenter knows that the critical path lies in full compliance with all of the clear CGMP *minimums* that, *contrary to the current practice*, clearly cover said products certainly from the moment they are first administered to humans and, *in all probability*, from the moment they are given to human-related animals (primates) until the last batch of each medical product is accepted and distributed.

In the past two years, the Agency has:

- A. Failed to require the medical products industry to fully comply with all of the applicable CGMP strictures in several key areas,
- B. *In the areas of NME and NME-based medical product submissions, Process Analytical Technology (PAT), and the uniformity assessment of solid dosage forms*, has gone so far as to issue draft guidances that are, *on the whole*, clearly at odds with the applicable CGMP regulations – in spite of the fact that in 1988 the US Supreme Court (**Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**) unanimously ruled that publishing a document that are at odds with any clear regulation is illegal, **and**
- C. Continued to knowingly permit the release of batches of CGMP-covered drugs, including biologicals, whose acceptance release failed to fully comply with the clear mandates of **21 CFR 211.165(d)**.

The Agency’s actions and inactions have only served to encourage the medical products industry to cut corners because, to date, the costs to the firms who have been found to be deficient have been significantly less than the additional profits earned by knowingly operating in a manner that does not meet the clear CGMP *minimums*.

As long as the medical products industry is allowed to operate as they currently do and pass whatever costs they incur onto the public, this industry will have little, if any, incentive to produce CGMP-compliant products or, for that matter, contain their costs.

As the industry spokesperson’s comments clearly indicated on the recent “**60 Minutes**” segment, today’s medical products industry believes it has the “right” to maximize its profits regardless of the impact of their actions upon the public health.

If the public doesn’t like that reality (e.g., with respect to antibiotic products), the industry representative’s position was that the public should directly pay

the industry to develop the new medical products needed to preserve and maintain public health in such “low profit” areas.

Given the current level of arrogance by the medical products industry that such remarks convey towards the consumer, it is obvious to this commenter that the Agency’s highest priority should be to rein in this arrogance by strictly requiring all medical products firms to fully comply with all applicable CGMP **minimums**.

Moreover, *when such firms are found to have knowingly failed to comply with said CGMP **minimums***, the FDA should direct the Department of Justice to proceed against both such firms and their senior management under the criminal sections of the “Racketeering, Influencing, and Corrupt Organizations” (RICO) statutes instead of asking the Department of Justice to pursue consent decrees and negotiated fines that:

- a. *In almost all cases*, do not come close to the added profit that was or will be earned by the offending firm who has knowingly chosen not to comply **and**
- b. *In any case*, will be subsequently recovered by the affected firm through overall price increases for the firm’s medical product lines.

“A Better Product Development Toolkit Is Urgently Needed

It is clear to FDA scientists, who have a unique vantage point and experience base, that a better product development toolkit is urgently needed. The Agency oversees all U.S. human trials and development programs for investigational medical products. As part of its regulatory role, FDA works with the scientific community to set the clinical and technical standards used in development. During the clinical phases of product development, Agency scientists conduct ongoing reviews of product safety, efficacy, and quality data. At the marketing application stage, data submitted by medical product sponsors are evaluated against the established scientific standards. FDA scientists are in frequent communication with industry and academic scientists over development issues (Figure 7). Agency reviewers see the successes and associated best practices as well as the failures, slowdowns, barriers, and missed opportunities that occur during the course of product development. In addition, data on product testing, safety evaluation, and clinical trials are stored in the millions of pages of FDA files. FDA reviewers oversee the totality of the preapproval development process. Because of this perspective, FDA reviewers are in a unique position to help identify common themes and systematic weaknesses across similar products and can draw important lessons from what they see.

While it is true that the FDA personnel “have a unique vantage point and experience base,” it is also true that these are limited:

1. To the information provided to the Agency (and, as this commenter well knows, a) firms may and have knowingly withheld certain key information from the Agency, b) the information furnished is derivative information presented in the most “favorable” light, and c) the information is usually not sufficient for the provider or the Agency to

make a 95%-confidence-level population-representative assessment of its probable scope and import.

2. By the failure of:

- a. The test samples evaluated to be:
 - i. Representative of the product batch from which they were taken **and/or**
 - ii. Sufficiently uniform.
- b. The experimental design to test sufficient population representative samples a sufficient number of times across the appropriate subject population to ensure that the results obtained are predictive of the current state of affairs at a confidence level of 95% or higher.
- c. The scientists designing and performing the experiments and evaluations to truly understand and apply the fundamental tenets of statistics based experimentation and experiment evaluation.
- d. The industry scientists who evaluate the test results obtained to do so in a manner that does not bias or obscure the true nature of the outcomes and/or the limited nature of their predictive power (in terms of both confidence level and population coverage).
- e. The Agency scientists who examine the information provided to:
 - i. Have the requisite statistical knowledge, training and experience,
 - ii. Understand, and make appropriate allowances for, the preceding industry deficiencies and proclivities, **and**
 - iii. Examine the raw results information rather than the “massaged” and “structured” findings presented to the Agency.
- f. The Agency to require that all studies in which humans are the subject be conducted under and meet all of the applicable CGMP minimums including, but not limited to, those that require the samples tested to be:
 - i. *Scientifically sound,*
 - ii. *Batch representative,* **and**
 - iii. Sufficient in number to predict *probable* population outcomes at a confidence level of 95% or higher.

3. By:

- a. The Agency’s pervasive lack of understanding of the value and import of requiring:
 - i. The medical product samples sampled to be highly uniform, batch representative, and produced by a process that, from the inputs onwards, is scientifically sound, appropriately controlled and reproducible,
 - ii. The samples tested to be population representative and sufficient to be population predictive at a confidence level of 95% or higher,
 - iii. The use of valid distribution-free statistical techniques unless the near-normality of the population has been established, **and**

- iv. Sufficient replicate testing to separate the sample-related results from the sampling- and test- related “evaluation” uncertainties (noise) inherent in the experimental designs and evaluation procedures used.
- b. The FDA’s historical failure (*during their development, submission, pre-approval, approval, and post-approval reviews and audits*) to detect that key adverse findings by the industry have been an/or are being knowingly kept from the Agency – including, *but not limited to*, adverse animal studies (e.g., Accutane), results that cast doubt on the reproducibility of the product tested or the scope of the outcomes observed, and pre- and post- approval adverse findings – either completely or for significant periods of time.
- c. The lack of sufficient “institutional” knowledge awareness continuity – a problem that repeatedly leads to the Agency’s having to relearn the same information.
- d. The Agency managers’, reviewers’ and auditors’ apparent lack of training in and understanding of:
 - i. All applicable aspects of sound statistical science including, but not limited, to: statistical fundamentals, experimental design, sampling, sample evaluation, sample statistics, population statistics, uncertainty analysis, population coverage, confidence, and probability,
 - ii. The applicable CGMP and other regulations that bear upon any decision they may make, **and/or**
 - iii. Medical product manufacturing, inspection science, and *statistical quality control* since, under CGMP, these apply to each batch, lot or shipment for incoming components, process controls, in-process materials, and medical products.

Based on this commenter’s knowledge and experience, the Agency’s stated views vis-à-vis the Agency’s “unique vantage point and experience base” are, at best, myopic.

They also ignore the fact that, in large measure, Agency personnel, bombarded by the industry and its consultants with a sea of carefully crafted positions and “pseudo-science filled” documents, are often led into adopting positions that are clearly at odds with some aspect of sound science and/or a clear applicable regulation.

For example, many in the Agency incorrectly believe:

- ❖ A valid in-house standard weight-percent purity can be assigned by performing a couple of Assays of the candidate material against the USP’s *Reference Standard* **or**
- ❖ The USP’s *IDENTIFICATION* tests are the “same” as the CGMP’s “identity” and “specific identity” tests.

Similarly, many in the Agency seem to incorrectly believe that the use of the USP sample numbers and specifications satisfies the clear requirements of **21 CFR 211.165(d)**.

Based on that false belief, these Agency personnel then approve submissions in which the drug-product's batch release controls and acceptance specifications are based on the post-release sampling plans and specification limits set forth in the USP's post-release, "any sample in commerce" drug and drug product monographs even though, *as even the USP has noted in its **General Notices***, such obviously do not meet the clear CGMP *minimums*.

Unable or unwilling to recognize that the true root causes of most of the problems are with the users and/or usage of the current tools and not the tools themselves, the Agency chooses to blame the "tools."

Blaming the "tools," the FDA then calls for "a better product development toolkit" rather than recognizing that what is truly needed is better use of the current "toolkit" by better-trained "tool" users.

After all, master carpenters using the simple hand tools crafted some of the finest furniture ever produced.

Moreover, *in spite of the availability of laser-guided power tools and trainable robotic manufacturing production lines*, even the best furniture produced today by such is of lesser quality than that produced decades and, in some cases, centuries ago by those master craftsmen who only had access to simple hand tools.

Furthermore, almost all of the FDA's archive of "data on product testing, safety evaluation, and clinical trials" ("stored in the millions of pages of FDA files") is derived from sample sets that are:

1. Non-population representative,
2. Uncertainty biased **and/or**
3. Fail to be sufficient in number to be predictive of the batch evaluated much less the population.

Usually, the data sets in the archive are of limited value because the results recorded are biased by their usually undisclosed evaluation procedure and measurement uncertainties and/or they are from non-representative samples.

Even if the Agency does not know this, the medical products industry not only most certainly does know this but also continues to adopt and advocate positions that are, *on their face*, at odds with sound science and/or CGMP compliance whenever doing so suits their readily apparent agenda to maximize their profit while minimizing their costs.

Medical products firms do this even when doing so is a knowing regulatory compliance failure upon the part of the medical product manufacturer.

While this commenter agrees that “FDA reviewers are in a unique position to help identify common themes and systematic weaknesses across similar products,” their apparent lack of the appropriate “education, training, and experience” (as required by **21 CFR 211.25** for drugs and biologics) or “the necessary education, background, training, and experience” (as required by **21 CFR 820.25** for medical devices) have obviously combined to weaken and restrict the Agency’s ability “identify common themes and systematic weaknesses across similar products.”

Thus, *at a minimum*, the Agency also needs to appropriately strengthen the education, training and experience of its personnel in the fundamentals of statistics, experimental design, inspection science, and the clear requirements of all of the CGMP regulations as set forth in **21 CFR Parts 210, 211, and 820**.

The FDA should do this in a manner that ensures the **scientifically sound** and **regulation-compliant** use of the current “toolsets” before it embarks on developing new “toolsets” that embody the same scientific, regulatory, and personnel deficiencies as those found in the current “toolsets.”

“Figure 7: Industry – Agency Interactions During Drug Development”

This commenter finds that this figure accurately illustrates the *formal* interactions between the “Industry” and the “Agency” during drug development.

“Few other groups of physicians and scientists are positioned to see so much of the broad picture. Of course, industry scientists encounter these problems in terms of their own product portfolios, but often lack cross-cutting information about an entire product area, or complete information about techniques that may be used in areas other than theirs. Academic programs focused on the medical product development process are rare and, at present, cannot be informed by FDA's broad experience with often confidential information. In fact, since the details of most failed programs cannot possibly be shared publicly or for applied research purposes, FDA holds the only broad, cross-cutting knowledge about how certain investigational products fail, why certain therapeutic areas remain underdeveloped, and when certain development hurdles persist despite advances in technology that could mitigate them. Indeed, these failures may trigger regulatory actions such as putting *clinical holds* on human trials, or turning down applications. In the course of such an action, FDA identifies problems and offers advice on how to overcome them. Advice given to product developers is based on FDA’s experience with the totality of other applications and FDA’s efforts to keep up with the latest science; it does not reflect specific proprietary information from individual applications. Despite these efforts, the

ability of product developers and FDA scientists to overcome development challenges is often confounded by the limitations of current tools to address development challenges.

While this commenter agrees in principle with much that the Agency states here, this commenter must again note that, *in order of importance*, **a)** non-robust processes, **b)** knowingly deficient studies, **c)** concealed and slanted information, and **d)** the Agency personnel's lack of appropriate knowledge and understanding (or **e)** their personal "political" agenda) are much greater limitations to "the ability of product developers and FDA scientists to overcome development challenges" than the Agency's perceived "limitations of current tools to address development challenges."

"Agency reviewers see the successes ... failures ... and missed opportunities"

This commenter understands that what the Agency really sees is, *as with any development process designed to produce and market a product, be it commercial or theatrical*, limited by the "scenes" provided to it by the developers of that process and product.

Hopefully, after reading this commenter's remarks and reviewing the records regarding some of the recent problem products that were approved and then withdrawn and others where concealed, missing or "massaged" information misled the Agency about either the true safety risks and/or costs to the public (e.g., Accutane, Fen-Phen, Premarin, and the Lyme disease vaccines), or about the product's risk/benefit ratio (e.g., Baycol, Cefixime, Paxil, Resulin), the Agency will have a better appreciation of the current limitations to their overall view of the medical products industry.

"Figure 8: Problem Identification and Resolution During the FDA Product Review Process"

This commenter agrees that the scheme outlined in the diagram provided depicts the approach the Agency uses to *attempt* to resolve a "problem" identified in the FDA's product review process.

However, the scheme outlined does not include specific outcomes "boxes" that explicitly address the Agency actions when the problem is resolved or, *more importantly*, the Agency's actions when a problem cannot be resolved within the allowable review framework.

As the text under the figure indicates, the figure actually shows "a cycle of problem identification and attempted resolution."

Based on the cycle that the figure actually outlines, this commenter suggests that the title for the figure should be changed to read "**Problem Identification and Attempted Resolution During the FDA Product Review Process.**"

“When the tools and concepts fall short, FDA works proactively with product developers and the scientific community to identify and resolve critical development problems and stimulate research, encouraging the development of solutions. The Agency often makes this information available to the public through guidance documents that synthesize current knowledge on approaches to development problems, or, as appropriate, through workshops, or peer reviewed publications (Figure 8). Guidance documents can also help ensure that FDA’s safety and effectiveness standards in a particular area of product development are up to date.”

While this commenter does not disagree with the FDA’s characterization of its activities per se, this commenter does note that, in the area of guidance documents, many of the recent drafts seem to be heavily industry influenced or generated documents that: **a)**, *in many cases*, do not conform to the clear minimum requirements of the CGMP regulations **and b)**, *where these drafts are supposed to be “science based,”* they are instead knowingly based on weak science, or non science presented as science.

Until these obvious deficiencies are corrected, these clearly violative (**Berkovitz, Plaintiff v. United States [486 US 531, 100 L Ed 2d 531, 108 S Ct 1954]**) drafts do more to undermine the regulatory process than they do to “help ensure that FDA’s safety and effectiveness standards in a particular area of product development are up to date.”

Moreover, the Agency’s continued acceptance of the submission of data from non-population-representative and low-confidence studies and evaluations does little to reduce the risk of not only subsequent product problems for new products but also directly contributes to the “low productivity — measured by the high costs and high risks of failure in the current development processes and the declining number of successful products reaching patients.”

Hopefully, after carefully studying this commenter’s remarks, the Agency will alter its stance towards the acceptability of such non-population-representative and low-confidence studies and evaluations and require that, *except for initial screening trials*, all studies and evaluations must:

- Be appropriately population representative **and**
- Provide a confidence level of not less than 95% worst-case.

“Sponsors report that the availability of FDA guidance documents¹⁹ often substantially decreases uncertainties associated with product development. Our own research has confirmed this. For example, compared to device development lacking FDA guidance, medical devices developed in areas with extant FDA guidance documents are almost twice as likely to be approved after the initial review process and are approved in a third less time.²⁰ FDA has undertaken efforts to develop such guidances in some of the most crucial public health issues.

¹⁹ The Agency publishes 50 to 75 draft and final guidances each year, including guidances resulting from involvement in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

²⁰ FDA, 'Improving Innovation in Medical Technology: Beyond 2002,' January 2003."

While this commenter does not dispute the preceding findings, this commenter notes that often the industry provides the majority of the input to said "guidances" and, in effect, thereby effectively "greases the skids" in a manner that results in the outcomes observed ("compared to device development lacking FDA guidance, medical devices developed in areas with extant FDA guidance documents are almost twice as likely to be approved after the initial review process and are approved in a third less time").

In many cases, these guidances amount to little more than a pre-negotiation between the Agency and the medical products industry as to what the Agency can be persuaded to accept even when that is less than the statutory CGMP minimums require.

"There is currently an urgent need for additional public-private collaborative work on applying technologies such as genomics, proteomics, bioinformatics systems, and new imaging technologies to the science of medical product development. Properly applied, these new technologies could provide tools to detect safety problems early, identify patients likely to respond to therapy, and lead to new clinical endpoints. New medical technologies, including bioengineered tissues, cellular and gene therapies, nanotechnology applications, novel biomaterials, and individualized drug therapies, will all need new product development tools and standards, as discussed below, to be able to move from the laboratory to the market quickly and safely."

While this commenter mostly concurs with what is stated, this commenter notes that the Agency's wording "to move from the laboratory to the market quickly and safely" clearly indicates that the Agency is apparently continuing to place speed before safety.

"FDA works proactively with product developers and the scientific community to identify and resolve critical development problems"

This commenter agrees with the Agency here but notes that the FDA's proactive approach at times seems to be at the expense of the Agency's duty to protect the public health.

"There is also an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses. The NIH is addressing very important clinical research infrastructure problems in its Roadmap initiative, and FDA is collaborating in the Roadmap efforts. In addition, much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products.

This commenter fully agrees with the Agency concerning “an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses.”

Except for medical conditions for which there is no current therapy, all clinical trials, safety and efficacy, should be required to:

1. Replace the current placebo arm in all trials with either the most generally prescribed effective approved therapy or, where one therapy is clearly the more effective, the more effective therapy.
2. Enroll healthy individuals in all safety studies that, based on the enrollees, medical history and all information on the previously observed, expected or probable side effects, such studies:
 - a. Contain an expected-treatment-population-representative cross section of enrollees,
 - b. Normalize all safety dosings to the body mass of each enrollee so that each enrollee receives approximately the same dose per kg of enrollee weight,
 - c. Contain a treatment population representative distribution of the sex and age range that the treatment or device is designed to provide therapy for, **and**
 - d. Increase the number of enrollees in all safety trials beyond *the initial pre-screening ones* such that the number of enrollees is sufficient to:
 - i. Have not less than a 90 % probability of discovering evidence a “0.1% of the proposed target population” side effect,
 - ii. Provide a 99% probability of detecting a “10% proposed target population” side effect, **and**
 - iii. Furnish a 95% confidence level that the trial medical product has a safety profile that is not significantly worse (at $p = 0.01$) than the current approved therapy.
3. Safety studies must be conducted that include a highest-dose drug interaction study that adds those drugs that the population targeted by the new therapy is likely to be taking.
4. Based on the outcomes from all safety trials, all efficacy studies should be three-armed (the chosen “more effective” approved therapy, and, based on safety studies, the lowest effective dose for the trial therapy, and the highest tolerated dose for the trial therapy). In addition, the enrollee population in all efficacy studies should be adjusted to:
 - a. Mirror those sub-populations who are at most risk of having an adverse reaction to the therapy,
 - b. Reflect those sub-populations who are most resistant to the current approved therapy in the comparison arm,
 - c. *To the extent possible*, administer body-mass normalized doses to the enrollees in all arms of the trial, **and**

- d. Extend the trial to at least 150% of the time for the current approved treatment in the comparison arm (or, where there is no current approved therapy, to beyond twice the expected treatment period [based on the treatment interval for similar conditions]).
5. For medical products that are judged by “endpoints intended to evaluate the effects of medical products,” the endpoints for the currently approved therapy should be used as the endpoints for the trial therapy unless the firm has data that, *at a confidence level of not less than 99%*, clearly establishes that proposed alternative endpoints are more indicative of therapy effectiveness or there is no currently approved therapy that is comparable to the therapy furnished by the trial medical product.
6. In deciding the acceptability of any trial medical product,
 - a. *When there is a current approved therapy*, the data must clearly prove, *at a minimum confidence level of 97.5%*, that:
 - i. The trial medical product is at least as effective (within a 10 % plus/minus window) as the currently approved therapy **and**
 - ii. The short-term adverse effects profile is not significantly worse (within 20%) than the current approved therapy;
 - b. *When a placebo must be used*, the projected short-term adverse health effects do not include (at $p = 0.001$) the risk of death or (at $p = 0.01$) the risk of the triggering of severe non-reversible reaction to the patient population; **and**
 - c. *When the trial uses surrogate “treatment” endpoints rather than condition “prevention” or “condition cure” to measure efficacy*, attainment of the endpoint must not carry with it a significant risk ($p = 0.05$) of longer-term adverse outcomes (i.e., enrollees must be followed for an appropriate period beyond the end of the trial to judge the longer-term effects of therapy cessation including reversion to an existing approved treatment to check for adverse effects with delayed onset times).

This commenter notes that, for example, had these design changes been in place, the public would have certainly avoided the injuries and deaths caused by the FDA-approved “me too” cholesterol-lowering statin Baycol and, *in all probability*, the Fen-Phen combination for weight loss would not have been submitted for approval.

In addition, the Agency’s policy toward “me too” products should be hardened to require the submitters of such to prove, *at the 99% confidence level for all proposed recognized therapy sub-populations*, that the new “me too” is:

- ❖ As safe but more effective than the best existing approved therapy,
- ❖ As effective but safer than the safest existing approved therapy, **or**
- ❖ *If the new “me too” is as safe but no more effective than the best existing therapy*, the new “me too” must have a significantly narrower

drug interaction profile for those drugs likely to be given to the treatment population than the existing best approved therapy.

“Tools for Assessing Safety

For effective development, safety issues should be detected as early as possible, and ways to distinguish potential from actual safety problems should be available. Unfortunately, in part because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. One pharmaceutical company estimates that clinical failures based on liver toxicity alone have cost them more than \$2 billion in the last decade — dollars that could potentially be directed toward successful new product development.²¹”

While this commenter cannot dispute most of what the Agency is stating here, this commenter notes that, contrary to the Agency’s portrayal, the problems uncovered “after marketing” are almost always linked to the submitting firms deliberate minimization of the hints of said problems contained in the safety and efficacy studies conducted sometimes to the point that negative studies have been deliberately omitted.

However, if the Agency is truly interested in finding safety-related problems earlier, then the Agency need only require that:

1. The dosing or device items used in all trials be highly uniform and produced by a reliable well-controlled reproducible manufacturing process that meets all of the applicable CGMP minimums, **and**
2. A sufficient number of tests, *including repeats to determine subject, test, and testing variance contributions to each result value*, must be performed so that the data clearly provide, *at the 99% confidence level*, valid estimates for the safety profile of the trial medical product

“Sometimes, early tests suggest the possibility of safety problems that never materialize, potentially eliminating candidates unnecessarily. Many of FDA's targeted efforts to date have involved defining more reliable methods for early prediction and detection of significant safety problems. The Agency seeks to prevent harm to patients during clinical development as well as potentially devastating setbacks to a new technology’s progress and to public confidence.”

²¹ Rotman, D, ‘Can Pfizer Deliver?’ *Technology Review*, February 2004.”

In this commenter’s experience, the false indications of safety problems arise because the studies currently being performed are neither statistical sound nor designed to be able to separate the true response value from the raw response by using experimental designs that permit the 95%-confident removal of the uncertainty (variance) contributions (*factors linked to subject, test procedure, sample evaluation, and random errors*) from the raw result values.

This problem exists because the current experimental designs used are designed to minimize the testing at the expense of result accuracy confidence – a knowing cost minimization choice that is inherently risk taking rather than risk adverse.

Until these product and test uncertainty problems are directly addressed, the Agency will be faced with having to remove newly approved medical products from the market regardless of the “tools” used to assess the safety and efficacy during the development of that new medical product

“Tools for safety assessments include product testing (e.g., for contamination), as well as in vitro and animal toxicology studies, and human exposure. Despite some efforts to develop better methods, most of the tools used for toxicology and human safety testing are decades old. Although traditional animal toxicology has a good track record for ensuring the safety of clinical trial volunteers, it is laborious, time-consuming, requires large quantities of product, and may fail to predict the specific safety problem that ultimately halts development. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population was not representative of eventual recipients. Conversely, some models create worrisome signals that may, in fact, not be predictive of a human safety problem. Many of FDA’s recent targeted efforts have involved working with the scientific community to define more reliable methods to predict and detect significant safety problems. For example, in the past, failure to predict unfavorable human metabolism of candidate drugs has led to costly failures in the clinic as well as multiple drug market withdrawals. FDA recommendations on the use of human cell lines to characterize drug metabolic pathways provide a straightforward in vitro method for prediction of human metabolism, allowing developers to eliminate early on compounds with unfavorable metabolic profiles (e.g., drug-drug interaction potential). Failures in the clinic due to drug interaction problems are now far less likely.”

This commenter notes that: **a)** most of what is said is a more-detailed rehash of the Agency’s preceding comments **and b)** most of the problems presented could be resolved if the Agency were to implement the corrective actions suggested by this commenter.

Moreover, though the “use of human cell lines to characterize drug metabolic pathways ~~provide~~ provides a straightforward in vitro method for prediction of human metabolism, allowing developers to eliminate early on compounds with unfavorable metabolic profiles (e.g., drug-drug interaction potential),” the Agency’s failure to enforce full CGMP compliance and require the use of *statistical quality control criteria* that have a product-predictive 95%, or higher, confidence level in their predictive ability are still sufficient to lead to “failures in the clinic.”

“In another effort, FDA developed and standardized methods for documenting clearance of retrovirus-like particles from tissue culture fluids. This effort successfully addressed potential safety concerns that surrounded the early use of monoclonal antibodies and paved

the way for the development of many important medical treatments. Through its own laboratory efforts, FDA has continued to refine these methods, share them publicly, and reduce their cost.

Additional examples of FDA efforts are listed under Highlights on the following page.”

While this commenter applauds the Agency’s success in their initiatives, this commenter again notes that the “root” causes of many of the remaining problems can be traced to the Agency’s ongoing failure to mandate compliance adherence to, and audit to ensure full compliance with, all of the applicable CGMP minimums from the “**Pre-clinical**” stage onwards.

“Most of the tools used for toxicology and human safety testing are decades old”

And, as the text clearly indicates, some are new -- so?

This commenter fails to comprehend the reason this text was highlighted since it is not the age of the tool (for example, the “wheel” has existed for centuries) but its utility (but its use is essential and will be for the foreseeable future) and usage trend (the usage of wheeled vehicles is still increasing) that is of importance

“

Highlight: Tools for Assessing Safety

1. The need to ensure the safety of biological products by preventing contamination has resulted in numerous Agency research programs and resulting animal models, test methods, and technical standards.

- A reference standard for evaluating gene therapy vector contamination by retroviruses has been developed with FDA input and is being distributed by the American Type Tissue Collection (ATTC).
- In the wake of concern over the safety of gene therapies for genetic diseases, FDA developed an animal model for assessing the safety of adenovirus vectors.
- FDA developed several rodent toxicity models to assess the neurovirulence of live virus vaccines, an approach that has both reduced the use of primates for testing and sped the testing process.
- With the potential resurgent need for smallpox vaccination, FDA scientists developed a new technique to detect the presence of contaminating virus in smallpox vaccine products. This technique can also be applied to characterization of other vaccine and cellular products.

2. FDA collaborated with industry and scientific groups to develop the data that allowed international adoption of a transgenic mouse model for drug carcinogenicity testing. This assay takes less time, saves two thirds of the cost, and uses half as many animals as a traditional study.

3. FDA has mined its databases to develop structure-activity relationship software to help identify molecular substructures with potentially negative toxicologic properties early in the development process.

This commenter again lauds the Agency for its contributions to the preceding apparently successful initiatives that have resulted in better tools, but thinks, as well as hopes, the Agency will do more to guarantee that the development process fully complies with all of the applicable CGMP **minimums** – an area that both the FDA and the medical products industry have, for different reasons, knowingly neglected.

“Towards a Better Safety Toolkit

There are currently significant needs, but also significant opportunities, for developing tools that can more reliably and more efficiently determine the safety of a new medical product.

Examples of tools that are urgently needed include better predictors of human immune responses to foreign antigens, methods to further enhance the safety of transplanted human tissues, new techniques for assessing drug liver toxicity, methods to identify gene therapy risks based on assessment of gene insertional and promotional events, and efficient protocols for qualifying biomaterials.

Opportunity: Proteomic and toxicogenomic approaches may ultimately provide sensitive and predictive safety assessment techniques; however, their application to safety assessment is in early stages and needs to be expanded.²² Targeted research aimed at specific toxicity problems should be undertaken.

Opportunity: As biomedical knowledge increases and bioinformatics capability likewise grows, there is hope that greater predictive power may be obtained from in silico (computer modeling) analyses such as predictive toxicology. Some believe that extensive use of in silico technologies could reduce the overall cost of drug development by as much as 50 percent.²³

- FDA’s files constitute the world’s largest repository of in vitro and animal results that are linked with actual human outcomes data. Further datamining efforts that effectively protect proprietary data could form the basis for useful predictive safety models.
- Use of extant clinical data may help construct models to screen candidates early in the development process (e.g., for liver toxicity).

Opportunity: There is an urgent need to develop tools to accurately assess the risk of new drugs causing heart rhythm abnormalities. For instance, there are ongoing international efforts to develop, test, and validate nonclinical models that may be useful in predicting human risk. In addition, the clinical risks associated with a small degree of QTc interval prolongation need to be fully defined.

²² Petricoin EM, V Rajapaske, E H Herman, A M Arekani, S Ross, et al., ‘Toxicoproteomics: Serum Proteomic Pattern Diagnostics for Early Detection of Drug Induced Cardiac Toxicities and Cardioprotection,’ *Toxicologic Pathology*, 32(Suppl. 1):1-9, 2004.

²³ PricewaterhouseCoopers, ‘Pharma 2005 Silicon Rally: The Race to e-R&D’ Parexel’s *Pharmaceutical R&D Statistical Sourcebook 2002/2003*.

The above are only a few of the opportunities FDA reviewers and outside experts have identified.”

While this commenter accepts the validity of the opportunities in the examples provided, this commenter would have preferred to see the Agency include the missed opportunities in the safety area that are associated with the clear applicable CGMP-related **minimums** that the medical products industry continues to:

- Knowingly ignore **and**
- *In many instances*, pressure the FDA to go along with their knowing non-compliances.

“Getting to the Right Safety Standards

Because safety issues are a significant cause of delay and failure during development, some have advocated simply lowering safety standards. This is not a preferable solution. For ethical human testing, there is wide agreement that reasonable assurance of safety must be achieved before clinical trials begin. Patients, prescribers, payers, and the public share the expectation that marketed medical products will have a well-understood safety profile and a positive benefit/risk analysis. Today’s problems arise from the inability to confidently predict safety performance in a timely and efficient manner. Current tools are not only cumbersome, they are also imprecise and thus leave considerable residual uncertainty. The degree of uncertainty inherent in current techniques can result in conservative standard setting. We need new tools that can eliminate problem products early and can better predict ultimate safety performance. Applied critical path research provides the real opportunity for improving our ability to identify safety issues early and manage the remaining risks appropriately.”

This commenter would only add that much of the Agency’s purported “considerable residual uncertainty” can be attributed to the deficient experimental designs and sample inspection plans that the firms in the medical products knowingly choose to use since such minimize the firms’ costs and, *because of the deliberate* “imprecision” *introduced*, such often permit the firm to obtain quicker approval of the resultant lower-quality medical products than compliance with all of the applicable CGMP regulation **minimums** would allow.

“Tools for Demonstrating Medical Utility

Predicting and subsequently demonstrating medical utility (also called benefit or effectiveness) are some of the most difficult and important challenges in product development. Currently available animal models, used for evaluating potential therapies prior to human clinical trials, have limited predictive value in many disease states. Better predictive nonclinical screening methods are urgently needed. In many cases, developers must gamble on the results of the large-scale, expensive trials necessary to assess effectiveness in people. Such human trials are currently highly empirical, because most sources of variability in human responses are not understood and thus cannot be controlled for. It is clear to many in the field that new scientific advances have the potential to revolutionize clinical development. However, the path from scientific innovation to usable tool is not clear.

Better predictive nonclinical screening methods are urgently needed"

This commenter agrees with the Agency statements in this section of the text.

"FDA has identified a number of opportunities for targeted efforts in the area of effectiveness (see next section) and, where feasible, has undertaken targeted action. For example, FDA scientists developed statistical methods to control reader variability in trials of imaging devices and made the analysis software publicly available. Use of this method allows developers to reduce the sample size of imaging device trials by as much as 60 percent.²⁴ Similarly, FDA analysis of hypertension trials using automated blood pressure monitoring allowed for elimination of the placebo group in such trials.

²⁴ See, for example, Wagner RF, SV Beiden, G Campbell, 'An Approach to Multiple-Reader, Multiple-Case Receiver Operating Characteristic Analysis: Controversial – or Subtle?,' *Acad. Radiol.*, 2003, Oct; 10(10):1176-7; Wagner RF, SV Beiden, 'Independent Versus Sequential Reading in ROC Studies of Computer-Assist Modalities: Analysis of Components of Variance,' *Acad. Radiol.*, 2003 Feb; 10(2):211-2."

Contrary to the FDA's statement that FDA scientists have "developed statistical methods to control reader variability," this reviewer notes that statistical methods cannot "control ... variability"; such methods can only reduce or remove the variability contributions to the result values observed.

Otherwise, this commenter both recognizes and appreciates that the Agency has used statistical methods to correct raw results values for their variabilities and can only hope that the Agency will now compel the medical product industry to do likewise whenever such statistical methods can be, or are required to be, used to increase result precision and/or decision validity since the use of such statistical methods seems to be required by the applicable CGMP regulations (e.g., for drugs, **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” and **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,” as well as, for devices, **21 CFR 820**, “Subpart O—Statistical Techniques Sec. 820.250 Statistical techniques. (a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics. (b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented”).

“Adopting a new biomarker or surrogate endpoint for effectiveness standards can drive rapid clinical development. For example, FDA adoption of CD4 cell counts and, subsequently, measures of viral load as surrogate markers for anti-HIV drug approvals allowed the rapid clinical workup and approval of life-saving antiviral drugs, with time from first human use to market as short as 3.5 years. FDA convened the data holders, conducted analyses in conjunction with industry and academia, and provided guidance on trial design. Similarly, FDA adoption of the eradication of *H. pylori* as a surrogate for duodenal ulcer healing greatly simplified the path of those therapies to the market. FDA often approves vaccines based on their meeting validated surrogate markers for achieving protective levels of immunity. This greatly simplifies effectiveness studies, thus reducing time and costs.”

While the FDA’s portrayal of the AZT example may be accurate, this commenter knows that the realities associated with the ulcer and vaccine examples are much less “rosy” than the Agency’s rhetoric indicates.

In the “*H. pylori*”/“ulcer” case, it took the medical and healthcare industries more than a decade to agree upon an effective treatment regimen and the current most-prescribed prepackaged FDA-approved combination product, Prevpac[®] (consisting of Amoxicillin, Clarithromycin, and Prevacid[®]), has a single-therapy-regimen cure rate in 80% range instead of the more-effective three-product combination, Carafate[®], Prevacid[®], and the antibiotic that “Antibiotic Sensitivity” screening tests show is most effective against the strain of *H. Pylori* that the patient has – which has single-therapy-regimen cure rate in excess of 95%.

Further, the treating specialist physicians tend to insist that the patient to undergo an endoscopic exam before each treatment regimen to verify the presence of the ulcer initially.

Though all of the drugs used were approved for use and, in the early 1980’s, an Australian researcher had proven that *H. pylori* was the causative agent for simple gastric and duodenal ulcers and that giving a

single two-week treatment regimen to the patients that consisted of an acid blocker, an antibiotic to which the patient's *H. pylori* is susceptible, and Carafate® cured almost all such simple ulcers, the industry and the Agency took until 1996 (more than a decade later) to agree on a standard "treatment" regimen.

Further, *for non-obvious public-healthcare reasons*, the medical products industry has chosen to promote and the medical profession to adopt a lower cure-rate ("80%") regimen rather than the less-prescribed higher ("90%") cure-rate regimen, or the rarely prescribed highest ("95+%") cure-rate regimen described above. [Note: The following outlines one the "ulcer" examples that this commenter has some knowledge of:

- In 1997, patient given one regimen of PrevPak with 1-mg Prilosec once a day for 14 days);
- In 2000, when the condition again flared up, patient again given PrevPak regimen and told to take Pepto-Bismol tablets along with the regimen
- In 2003, patient given alternate therapy (Walgreens Smootie Tablets {generic "Pepto-Bismol" tablets}, 2 tablets four times a day, 500-mg Metronidazole tablets three times a day, 500-mg Tetracycline tablets four times a day, and 1-mg Prevacid once a day for 14 days) {Notice: When this treatment failed, specialist advised patient just to take Nexium for the rest of the patient's life};
- Other bridging treatments prescribed during this time period include: **a)** 1-mg Prilosec for 3 months, **b)** 40-mg Nexium Capsules twice a day (before AM and PM meal) for 1 week if not better, add in Axid (Nizatidine) at bedtime, and **c)** Carafate (instead of Nexium and Axid) four times a day, **and**
- Currently, self-prescription of 2 capsules of "Mastic Gum" (a homeopathic curative) in AM before breakfast with Prilosec OTC and a container of yogurt at breakfast for 14 days followed by continuing yogurt with an occasional Prilosec OTC when job stress is high followed by a reversion to the "Mastic Gum, Prilosec, yogurt" regimen if symptoms should persist.

{Notice: In addition, patient has been "scoped" twice with no conclusive findings and one "contaminated endoscope related" throat infection (the antibiotic given to treat the infection did suppress the patient's symptoms while the patient was taking it. Even when the patient requested being given the most effective curative regimen, the prescribing physicians declined to collect the requisite samples, authorize the appropriate the Antibiotic Sensitivity tests, and based on the test findings prescribe the most-effective combination of drugs (Carafate, appropriate antibiotic, and acid blocker) and diet (yogurt four hours after the first daily doses of the Carafate, antibiotic and acid blocker) daily for a period of not less than 28 days.}]

Thus, even today, patients with simple ulcers are usually not provided the best curative therapy but, instead, are offered less effective curative regimens that, *in cases where they fail to be effective*, turn into a recommendation for a lifelong symptom-control treatment program – a win-win situation for the pharmaceutical and "healthcare" industries.

In the vaccines area, the Agency approved the "Lyme disease" vaccines based on a surrogate endpoint of an "antibody titer."

Not only did these vaccines not provide the limited protection advertised but their “recognized but downplayed” auto-immune “side effects” turned out to be worse than the disease in many who were administered the vaccine.

Again, rather than being safe and effective, these vaccines furnished another win-win situation for the pharmaceutical and “healthcare” industries.

“Highlights of other recent FDA efforts are provided on the following page. Although there are many examples of successful outcomes, similar efforts are needed in many other areas of product development to improve the process for getting safe and effective new treatments to patients.”

This commenter agrees with the Agency here.

“Towards a Better Effectiveness Toolkit

We believe targeted efforts in a variety of areas could substantially improve the efficacy toolkit. These efforts, a few examples of which are listed here, can only be successful with the collaboration of industry, academia, and the patient and health care communities.

Highlight: Answering the Challenge of Bioterrorism — Evaluating Efficacy

With the increasing challenges of bioterrorism, there is both a need and an opportunity for animal models that are relevant and predictive of countermeasure effectiveness in humans, since effectiveness testing in humans is often not feasible. In some cases, approval can be granted on the basis of animal model findings. FDA and its partners can play a major role in both developing such models and helping define appropriate and efficient pathways for their use in product development. Such efficiency is critical both for proper stewardship of what are often limited or ethically sensitive animal resources, as well as for ensuring reliable threat preparedness in a timely manner.

- FDA developed an immunocompromised mouse model for studying the efficacy of treatments for smallpox vaccine side effects.
- FDA defined appropriate animal studies to evaluate the efficacy of next generation anthrax vaccines.
- Working with government and academic scientists, FDA developed protocols for the efficient use of animal models to evaluate antimicrobial efficacy against bioterrorist threat agents.”

Though this commenter does not agree with the Agency’s statements, this commenter understands that the jury is still out on *general* utility of this efficacy evaluation approach.

“Highlight: Trial Design for Digital Mammography — Overcoming Clinical Trial Hurdles

Although the initial approval of digital mammography did not include this claim, it was believed that digital techniques would prove more accurate than the conventional screen film. A 40,000-patient study would be needed to evaluate this. No company was able to do a 40,000-patient study. FDA proposed a trial in which four companies would each do a study of 10,000 patients, using a common protocol. The National Cancer Institute (NCI) was willing to conduct the study. The results from the four arms of the study could be pooled. The pooled trial will be able to test whether digital mammography is superior to conventional screen-film, and each firm will be able to use results from its own product. The trial costs have been shared among the companies and the NCI. The trial is completely enrolled and in the 1-year follow-up phase.

”

While this commenter lauds the Agency’s initiative even though, to get the industry to “go along,” the government is picking up some of the costs, this commenter notes that the jury is still out on whether this initiative will be successful in the long run.

“Opportunity: FDA actions and the subsequent passage of the ‘Best Pharmaceuticals for Children Act’²⁵ have spurred a significant increase in the number of pediatric studies of pharmaceuticals. Although the results of each individual trial have been informative for the particular drug studied, a significant opportunity now exists for analysis of what has been collectively learned about the pharmacokinetics, pharmacodynamics, safety, and efficacy of drugs in children. Such an analysis could begin to build a knowledge base to better inform future pediatric studies.

Because the products tested, experimental designs, and data sets collected continue to be statistically deficient and, in some cases, do not meet the applicable CGMP **minimums**, this commenter is properly concerned that the information garnered for the proposed study may be not only less than accurate but also, in some cases, misleading.

This commenter again counsels the Agency to begin vigorously addressing this area because of its importance not only for a given new product but also for the validity of the generalizations derived from the data sets for all of the trial products analyzed.

“Opportunity: ‘The appearance of new quantitative measuring technologies absolutely galvanizes new drug research.’²⁶ Additional biomarkers (quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development. In some cases, datamining and analysis, with possibly a single additional clinical trial, may be all that is necessary to confirm the surrogacy of a particular marker. In other cases (e.g., the NIH’s Osteoarthritis Initiative²⁷), epidemiologic studies on disease natural history must be undertaken to provide data on markers of disease processes. For biomarkers that currently appear promising, specific projects need to be undertaken to:

- Assemble existing data on the association of the marker with clinical outcomes

- Assemble existing data on the performance of the marker during intervention trials compared to the performance of current outcome measures
- Identify any data gaps or remaining uncertainties
- Identify clinical trials under development in which the remaining questions could be addressed in a straightforward manner”

²⁵ Public Law 107-109, Jan. 4, 2002.

²⁶ Niblack J, ‘Biomarkers and Surrogate Endpoints,’ GJ Downing, ed. *Exceptional Medical Int. Congress Series*, 1205, Elsevier, 2000.

²⁷ See <http://www.niams.nih.gov/ne/oi/>.”

Provided this commenter’s previous concerns are appropriately addressed, this commenter agrees with the FDA here.

“As previously stated, strengthening and rebuilding the disciplines of physiology, pharmacology, and clinical pharmacology will be necessary to provide the capacity to develop and evaluate new biomarkers and bridge across animal and human studies.”

Provided this commenter’s previous concerns are appropriately addressed, this commenter agrees with the FDA here.

“The appearance of new quantitative measuring technologies absolutely galvanizes new drug research”

This commenter finds the Agency’s rhetoric here to be more hype than substance.

“Opportunity: Imaging technologies, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals, but their predictive value needs further study and evaluation. New imaging technologies will ultimately contribute important biomarkers and surrogate endpoints, but how soon these new tools will be available for use will depend on the effort invested in developing them specifically for this purpose.

Opportunity: For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products. Much work needs to be done on clinical trial design and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization.

Opportunity: The concept of model-based drug development, in which pharmacostatistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision making.²⁸ Model-based drug development

involves building mathematical and statistical characterizations of the time course of the disease and drug using

²⁸ Sheiner LB, 'Learning VS Confirming in Clinical Drug Development,' *Clin. Pharmacol. Ther.*, 1997, 61:275-291.

available clinical data to design and validate the model. The relationship between drug dose, plasma concentration, biophase concentration (pharmacokinetics), and drug effect or side-effects (pharmacodynamics) is characterized, and relevant patient covariates are included in the model. Systematic application of this concept to drug development has the potential to significantly improve it. FDA scientists use, and are collaborating with others in the refinement of, quantitative clinical trial modeling using simulation software to improve trial design and to predict outcomes. It is likely that more powerful approaches can be built by completing, and then building on, specific predictive modules.

There are many important additional opportunities in the area of clinical trial design and analysis. More clinically relevant endpoints need to be developed for many diseases. Enrichment designs have the potential for providing much earlier assurance of drug activity. Bayesian approaches to analysis need to be further explored.”

Provided this commenter’s previous concerns are appropriately addressed, this commenter again agrees with the FDA here.

“Opportunity: The emerging techniques of pharmacogenomics and proteomics show great promise for contributing biomarkers to target responders, monitor clinical response, and serve as biomarkers of drug effectiveness. However, much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used. Specific, targeted efforts could yield early results.”

Provided this commenter’s previous concerns are appropriately addressed, this commenter does not disagree with the FDA here.

“Getting to the Right Effectiveness Standards

In an era of concerns about health care affordability, we need to make sure that new medical products are effective and provide accurate up-to-date information about using them so patients and doctors can make smart decisions about health care. As health care costs rise, patients, medical professionals, and health care purchasers are all demanding more value from the medical treatments they use. With more treatments in development than ever before, finding better ways to demonstrate their effectiveness for particular kinds of patients is essential for making sure that all Americans get the most value from their health care dollars. The industrialization challenges posed by the demands of physical product design, characterization, scale-up, and manufacturing are often little understood outside of FDA and the pharmaceutical and device manufacturing communities.²⁹ Many product failures during development are ultimately attributable to problems relating to the transition from laboratory prototype to industrial product. It is crucial that technical standards (e.g., assays, procedures, or reference standards) and improved methods for

design, characterization, and product manufacture are available to improve predictability in this area.

²⁹ See, for example, the Washington Fax interview with John La Montagne, Deputy Director of the National Institute of Allergy and Infections Diseases, National Institutes of Health, June 9, 2003.”

While this commenter is glad to see that the Agency has forthrightly stated the reality that most of the new medical products are “better” treatments (“With more treatments in development than ever before, finding better ways to demonstrate their effectiveness for particular kinds of patients is essential for making sure that all Americans get the most value from their health care dollars”), this commenter notes that the American public would be better served if more of the therapies approved prevented or cured a condition rather than, *as the trends indicate*, “better” and certainly more costly treatments that the patient must take for long periods of time.

From a cost perspective, while the public needs better preventive and curative therapies, the obvious greed-driven medical products industry, as a whole, is more interested in providing better treatments rather than condition prevention and disease cure.

If the Agency is truly interested in “making sure that all Americans get the most value from their health care dollars,” then it needs to use the muscle of its public health protection mandate to ensure that those medical products that offer prevention and cure are given priority over those that simply provide, at best, a more expensive treatment that, overall, may not provide any significant benefit over the currently available treatments (and, in some cases, ends up providing a lesser benefit [e.g., **a**] the case of the newer blood-pressure lowering medicines that are less effective than the previous generation’s chlorthalidone to the extent that the industry, *worried about losing their more lucrative products*, has introduced even costlier combination products that have no significant advantage over chlorthalidone and recently touted a questionable study that showed that patients taking chlorthalidone had a higher (“9%”) risk of developing diabetes than the newer drugs’ “7 %” risk; **or b**) the case of a new class of pain killers (COX-2 inhibitors) that have turned out to have, in general, no more efficacy or safety to the general patient problem than enteric coated aspirin – yet this reality has not prevented the industry from conducting a direct-to-the-consumer advertising program touting the ephemeral “advantages” of such over aspirin to the point that one firm’s slogan is “---, take it for pain, take it for life” – even though, overall, OTC aspirin provides more health advantages and fewer adverse side effects than this newer, more expensive, prescription drug product for much of the public]).

“Tools for Characterization and Manufacturing

Highlight: Industrialization

In the area of medical devices, blood glucose monitors represent a critical technology for many of the 16,000,000 diabetics in the United States. Numerous new devices are being developed for blood glucose monitoring.

- FDA helped develop a uniform testing protocol to evaluate glucose meter performance and compared the measurements to the hexokinase (HK) laboratory method incorporating reference materials developed by the National Institute of Standards and Technology.
- It was determined that separate accuracy and precision goals should be defined for extreme ranges to keep pace with changing clinical demands for tighter glucose measurement.¹

¹ Chen ET, JH Nichols, SH Duh, G Hortin, ‘Performance Evaluation of Blood Glucose Monitoring Devices,’ *Diabetes Technology & Therapeutics*, 5(5):749-768, 2003.”

This commenter has no problems with the Agency’s text here and is all for improved analytical tools.

However, recognizing and addressing the non-uniformity of the variance across the patient’s glucose levels is not a new tool.

Factually, variance-weighted data fitting is an existing decades-old tool.

“Highlight: Industrialization Standards

Together with CDC and industry, FDA was able to help make available difficult-to-obtain standards and samples needed for the successful rapid development and evaluation of West Nile Virus nucleic acid blood donor screening.

This commenter again lauds the FDA for assisting the CDC and the industry in developing a valid test for the screening of donated blood for contamination with transmissible West Nile virus.

“Developing interim standards is especially important for novel technologies and can help keep product development on track as a new field matures. Otherwise, innovators are put in the position of having to invent standards in addition to inventing new products. At the same time, interim standards must allow for flexibility, innovation, and change as new fields develop. This takes expertise, effort, and collaboration among industry, academia, and FDA.

For example, recombinant proteins and monoclonal antibodies have provided significant therapeutic advances over the last 15 years. During this time, FDA has issued multiple technical guidance documents on topics such as characterization of production cell lines, manufacturing and testing techniques, specifications, stability evaluation, and changes to manufacturing processes.³⁰ Recent guidances address the use of transgenic animals or bioengineered plants as production methods for such products. As new industrialization

challenges are identified during the review process, Agency scientists routinely hold scientific workshops, conduct research, collaborate with academic and industrial scientists and synthesize the emerging data. Recently, when safety problems developed with gene therapy adenovirus vectors, the need for a better potency standard was recognized. FDA collaborated with industry and governmental partners to develop the currently available reference standard for characterization of adenovirus vectors. To stimulate the needed vaccine development efforts, FDA scientists recently developed a breakthrough synthetic technology for conjugate bacterial vaccines that increases yields three fold and also lowers costs. For additional examples, see Highlights on the adjacent page.

³⁰ See Agency guidances at <http://www.fda.gov/opacom/morechoices/industry/guidedc.htm>.”

This commenter finds the Agency’s stated actions both appropriate and laudable.

“Rapid, successful development of new medical technologies depends on the ... availability of adequate methods to characterize, standardize, control, and mass produce them”

This commenter agrees.

“Towards a Better Manufacturing Toolkit

Rapid, successful development of new medical technologies depends on the concomitant availability of adequate methods to characterize, standardize, control, and mass produce them. Applied research in these areas is required to provide the infrastructure necessary for translating laboratory prototypes into commercial products. There are a number of urgent needs in the industrialization area. FDA is actively working on guidance in many of these areas to the extent permitted by available resources.”

This commenter does not disagree with the Agency’s statements in the preceding paragraph.

“Opportunity: Additional characterization procedures and standards for expanded stem cell and other cellular products, bioengineered tissues, and implanted drug-device combinations (e.g., drug eluting stents) are urgently needed. For example, developing test standards for coronary stent compressibility will decrease the likelihood of failed designs and allow smaller clinical trial programs.”

While, in general, this commenter does not disagree with the Agency’s preceding statements here, this commenter is not certain that developing the standards in question will necessarily “allow smaller clinical trial programs.”

Given the critical need to increase the confidence in trial outcomes so that, at a minimum, they are trial-product predictive at the 99% confidence level, perhaps the better position would be to emphasize that the standards in question might increase the confidence level in the outcomes observed for

the current clinical trial program size and, thereby, minimize the need to increase trial size to attain the indicated 99% confidence that the trial results are probably predictive of the “in use” post-approval outcomes that will be observed.

“Opportunity: The pharmaceutical industry generally has been hesitant to introduce state-of-the-art science and technology into its manufacturing processes, in part due to concern about regulatory impact.”

This commenter respectfully disagrees with the Agency.

Based on this commenter’s knowledge and experience, the principal impediments to introducing state-of-the-art science and technology are, and have been:

- ❖ The industry’s general opposition to operating under *scientifically sound statistical quality control* **and**
- ❖ The increased capital costs of such systems.

Moreover, the main “concern about regulatory impact” is the industry’s almost certain knowledge that proper implementation of said state-of-the-art science and technology will uncover more CGMP compliance problems than it addresses.

For example, *given the industry’s obvious non-scientific and CGMP-violative recommendations for assessing batch uniformity for processes that produce solid dosage forms that the FDA mostly incorporated into the clearly CGMP-violative draft guidance the Agency issued purporting to address said uniformity assessment*, it should be clear to all truly knowledgeable scientists that the industry is intent upon substituting pseudo science and inappropriate standards, specifications, and inspection plans for the “... scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (**21 CFR 211.160(b)**) that the clear CGMP regulation *minimums* (**21 CFR 211. 1(a)**) plainly require.

Moreover, the FDA’s going along with so obviously CGMP-violative recommendations demonstrates that the Agency either:

- ❖ Does not have the scientific and/or regulatory competence required to understand that the industry-backed proposal is at odds with several clear CGMP requirement *minimums*, **or**
- ❖ *Because of “political” reasons*, has decided to go along with most of the industry-backed proposal even though, in so doing, the Agency has knowingly chosen to operate outside of boundaries established in the federal laws governing the conduct of the FDA (as unanimously decided by the US Supreme Court in 1988 in **Berkovitz, Plaintiff v. United States [486 US 531, 100 L Ed 2d 531, 108 S Ct 1954]**).

Moreover, it would seem that, *by engaging in such actions*, the FDA calls into question the Agency's motives in all of their position statements including this document as well as the Agency's "Critical path Initiative."

"This led to high in-process inventories, low factory utilization rates, significant product wastage, and compliance problems, driving up costs and decreasing productivity."

As a PhD Analytical Chemist with a track record of developing inexpensive valid high-throughput robust analytical procedures using what the Agency would characterize as "old" tools and technologies, this commenter cannot agree.

For example, when a firm wants to speed up the testing of batches of Penicillin VK granulation for their uniformity with respect to the Sodium Citrate coated onto the Penicillin VK, this commenter devised a rapid differential ion-selective electrode method that, by using parallel weighing, dilution, and testing allowed samples to be screened at the rate of 55 per hour or 1 per minute and permitted Quality Control Unit (QCU) to review the valid *batch-representative* test results and determine whether or not a given batch was releasable within two (2) hours of the time the granulation was discharged from the granulator (within the 3-hour-plus post-granulation drying window). **[Note:** The initial batch screenings found that, because of the manner in which the product was granulated, the granulations were not uniform, and, after the QCU investigated, assisted the firm in rapidly revising the granulation procedure in a manner that rendered the granulations uniform to within +/- 2% of the target level of citrate worst-case. By contrast, the previous citrate assay method not only took hours to properly test a single batch but also had a significantly higher uncertainty that had caused the firm to adopt an abbreviated sampling plan and Assay testing that obscured the non-uniformity (which led, in turn, to portions of each released batch not having the stability they were represented to have). **In another example**, in the 1980's, *before the advent of rapid-scan UV/Visible spectrophotometers equipped with component deconvolution software (in the mid 1990's)*, this commenter helped develop a rapid dual-wavelength analytical method for the drug combination Sulfamethoxazole and Trimethoprim that: **a)**, using a Model Cary 219, allowed the uniformity of a suspension formulation to be accurately and rapidly assessed with minimal sample preparation at a rate more than ten (10) times faster than the USP HPLC method **and b)**, because of the instruments "0 to 5+" Absorbance-Unit linear range, could be used for all testing including the requisite dissolution test – *even though cross-verification showed the methods were comparably precise and the Cary method was significantly more accurate and rapid*, the FDA, *without having any scientifically sound or regulatory basis*, objected to that method's use for in-process and release testing and insisted that the firm use the USP method essentially because it was the USP method. As a third example, this commenter has time and again been faced with FDA personnel who: **a)** insist that secondary standard "purity" values should be assigned by comparative "Assay" testing against a USP **Reference Standard and b)** ignore: **i)** the +/- 2+ % uncertainty in the value that the procedures they advocate **and ii)** the fact that, in some cases, the "secondary standard" material prepared was, by impurity profiling and impurity

testing, purer than the USP **Reference Standard** – thus clearly demonstrating to this commenter: **a)** the Agency’s lack of competence in understanding the determination of material purity **and b)** its myopic view of result values that ignores value uncertainty. {In an attempt to address this issue and the others raised, this commenter has, at minimal expense to the FDA, repeatedly provided the Agency with the scientifically sound approaches to determining purity as well as all the other scientific issues raised by this commenter to little apparent avail – at least in the near-term in the Agency’s overall mindset though a few Agency personnel, having reviewed this commenters docket comments, white papers, discussion group comments, publications, and presentations, now seem to understand the difference between sound science and many of the industry-fostered non-science positions that permeate the Agency.}]

“FDA has led an initiative to stimulate the use of process analytical technologies — automated sensors that monitor and control processes — and other modern manufacturing technologies that can improve efficiency and increase flexibility while maintaining high-quality standards. Further research and data sharing are necessary to make these efficiencies a reality.”

While this commenter would agree that, *in the FDA*, CDER’s Office of Pharmaceutical Science seems to be promoting “process analytical technology” (PAT), *based on the draft guidance this office has issued*, this “FDA” initiative is not only scientifically flawed and does not conform to the clear requirement **minimums** of CGMP, but also this “FDA” initiative seems to be this office’s embracing a not so subtle attempt by the medical products industry to subvert and/or hijack the regulatory process by substituting pseudo-science for science and non-existent Agency discretion for CGMP compliance.

As the prior examples have clearly demonstrated, the current quantitative sample inspection tools that exist could be used to greatly increase the sample throughput without adopting any of the non-quantitative “PAT” tools and “automated sensors that monitor and control processes” being touted as the “wave of the future” for the drug and drug products portion of the medical products industry even though those who use such “tools” knowingly fail to take and evaluate sufficient truly *batch representative samples (in the range of a 100 samples across the batch for the non-discrete-material case and in the range of 1000 across the batch for the discrete-material case)* so that the “signature” inferences obtained comply with the applicable clear CGMP **minimums** and, therefore, can validly be used to predict the acceptability, or lack thereof, of the overall (unevaluated portion) of the batch (*typically, consisting of hundreds of thousands or millions of units*) being evaluated.

Moreover, most of the “modern manufacturing technologies” that can truly “improve efficiency and increase flexibility” in a manner that is CGMP compliant have existed for decades and have been in use in related industries for more than a decade.

For example, to increasing mixer utilization, a firm can switch from integrated mixer/mix containment systems to mixing systems where the batch is charged into a container that is then mated to a mixing head and then mixed.

In the first case, since in the integrated system the mixer must be cleaned, charged, used, and discharged for each batch, the available “mixing” time is only some small fraction of the total time (*typically, less than a third*) to produce a blend from start (loading) to finish (transfer of the last of the blend into its intermediate storage containers).

By contrast, in the non-integrated equipment case, one container can be being cleaned while another is being charged, a third is being mixed, and a fourth is being either transferred to holding or discharged to make way for its reuse.

In the second mode, even allowing for mixing head cleaning and maintenance, such systems have utilizations that approach 90 % -- or about two and a half times the limiting “efficiency” as the integrated mixer with no “mixer related” change in the quality of the product produced.

However, *because of the lack of rigorous scientifically sound and appropriate CGMP-compliant in-coming controls on the components that are mixed (that meet the clear requirements set forth in 21 CFR 211.84) and the process steps used (as required in 21 CFR 211 Subpart F--Production and Process Controls) well as the failure to establish scientifically sound and appropriate statistics-based specifications (as explicitly required in 21 CFR 211.110(b)) and rigorous in-process evaluation for acceptance or rejection during each significant phase of the production of each batch (as explicitly required in 21 CFR 211.110(c))*, the quality standards of most firms are much less than the “high quality standards” indicated by the Agency in the preceding paragraph.

Thus, contrary to the Agency’s assertion that further “research and data sharing are necessary to make these efficiencies a reality” all that is needed is for those that manufacture drug products to improve their efficiency is for said firms to implement these equipment redesign, improved control regimes, and full CGMP compliance initiatives outlined by this commenter though some of the newer techniques might, if implemented in a fully CGMP-compliant manner, further improve production efficiencies.

However, until and unless full CGMP compliance is mandated and today’s knowing non-compliant practices are eliminated, such drug products will continue to be substandard in quality and adulterated (*as that term is defined in 21 U.S.C. 351(a)(2)(B)*), instead of meeting the clear requisite CGMP quality standards much less the Agency’s claimed “high quality standards.”

“Opportunity: Scientists involved in reviewing medical devices at FDA report an urgent need for predictive software to model the human effects of design changes for rapidly evolving devices. We believe that such software may be attainable with a concentrated effort, by assembling currently available data and identifying existing data gaps.”

While there may be “an urgent need for predictive software to model the human effects of design changes for rapidly evolving devices,” what is truly critically needed is a better understanding of: **a)** the biological systems in which the devices are to reside, **b)** the interactions between and among the biological systems and the materials used in said devices, **c)** the implications and import of scale-model theory at the biological scale, **and d)** the underlying, often unobserved or indirectly observed, nano-scale phenomena occurring at the biological system’s interfaces with the device components.

Given the current lack of such understanding, at best, all that such “predictive software” can do is, *in favorable cases*, improve the empirical “guessing” process that seems to pervade much of today’s medical device development efforts. [Note: For example, considering the apparent short-term success of the “drug coated” and “drug releasing” arterial stents may or may not, *in the longer term*, lead to an improvement in the long-term success of such in improving cardiovascular health – in the absence of understanding, unintended long-term side effects may arise that outweigh the readily apparent short-term gains that such provide – only time and/or an understanding of all aspects of the cardiovascular system including, for example, its neurological and immunological aspects will let us know whether what appears in the short term to help reduce unwanted effects is truly beneficial long term.]

“Getting to the Right Manufacturing Standards

Problems with scale-up and mass production can also slow development and escalate costs. Currently, FDA is involved in an extensive, multi-year effort to incorporate the most up-to-date science into its regulation of pharmaceutical manufacturing and to encourage industry to adopt innovative manufacturing technologies.³¹ Moreover, we are also looking critically at areas where FDA regulation may have slowed adoption of improvements.

³¹ See ‘A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century’ at <http://www.fda.gov/cder/gmp/>.”

Since, based on: **a)** the FDA’s current repeatedly demonstrated lack of: i) understanding of the fundamentals of science in the areas of material science, material production, and material evaluation, **and ii)** requiring adherence to the clear acceptance-science-based requirements of the CGMP regulation **minimums** governing the manufacturing of drugs, drug products, and devices, **and b)** the Agency’s ready acceptance of industry-backed “recommendations that are knowingly filled with pseudo-science, ignore recognized consensus standards, cravenly misuse statistics, and, in

*many cases, deliberately ignore the clear science-based applicable CGMP , it is and should be clear to all that the FDA first needs to train itself to understand: 1) the fundamentals of science in the areas of material science, material production, and material evaluation, and 2) the clear acceptance-science-based requirements of the CGMP regulation **minimums** governing the manufacturing of drugs, drug products, and devices before even attempting “to incorporate the most up-to-date science into its regulation of pharmaceutical manufacturing and to encourage industry to adopt innovative manufacturing technologies.”*

After all, before attempting to rebuild a wooden house, one would do well to be trained in and understand the basics of sound carpentry.

Given that: **a)**, *based on their recent publications (notices, comments, speeches, and draft and final guidances)*, the majority of today’s Agency personnel have a biased, or no, understanding of such statistical basics as confidence, evaluation, probability, prediction, representative sample, and inspection (sampling and sample evaluation), much less practical experience in or understanding of product development, process development, analytical science, and statistical quality control, **and b)**, *based on the draft guidances being published today and the public remarks and comments made by said Agency personnel*, today’s Agency is often simply parroting the pseudo-science and misrepresentations knowingly used by industry to justify industry conduct that is clearly CGMP violative, the FDA has clearly demonstrated the Agency’s need to be trained in, comprehend, and apply the knowledge learned to, those areas of deficiency outlined by this commenter.

Further, *until the requisite scientific and regulatory understanding has been acquired, and the Agency can demonstrate, and has demonstrated, its willingness to use said understanding to truly protect the public health*, this commenter recommends that the Agency:

- Refrain from making any changes in its current CGMP regulations and
- Cease accepting any industry-sponsored initiatives that:
 1. Fail to fully comply with the clear CGMP **minimums**,
 2. Are not based on:
 - a. Any and all applicable recognized scientific consensus standards **or, in the absence of recognized consensus standards**,
 - b. The fundamentals of any and all applicable scientific disciplines, **and/or**
 3. Do not provide a detailed scientifically sound rationale, *based on the recognized fundamentals of inspection science*, that clearly establishes that the proposed initiative does provide:
 - a. *For drugs and drug products including biologicals*, a “population confidence level of not less than 95%” assurance that the

untested portion of *each batch* meets *appropriate batch acceptance criteria* prior to its release for distribution or,

- b. *For devices*, “an individual-device confidence level of not less than 99%” assurance that each device accepted for release fully complies with all of its acceptance specifications and criteria.

“The availability of efficient, science-based standards for product characterization and manufacturing creates a win-win for consumers, patients, and the industry.

Were truly “science-based standards for product characterization and manufacturing” to be made available and were the industry to adopt such “science-based standards for product characterization and manufacturing” in a manner that was directed towards the “efficient” production of *curative* and *preventive* therapies rather than “better treatments, then such would create a win-win situation for ” consumers, patients, and the industry.”

However, the Agency’s statements are, at best, confusing.

Science-based standards, *whatever their use*, have no intrinsic efficiency attributes, “efficiency” is determined by the manner in which valid science-based standards are implemented by the user.

Moreover, if the medical products industry chooses to efficiently implement such valid science-based standards but to direct the majority of their efforts toward “better treatments” rather than “cures” or “preventives,” *as today’s industry appears to be currently doing*, then, *while that situation may be a win-win solution for the industry*, it will, *at best*, be **win-lose** solution for consumers and patients.

“A Path Forward

Greater success along the critical path demands greater activity in a specific type of scientific research that is directed at modernizing the product development process. This critical path research — highly pragmatic and targeted in its focus on issues such as standards, methods, clinical trial designs, and biomarkers — is complementary to, and draws extensively from, advances in the underlying basic sciences and new technologies. Without a concerted effort to improve the critical path, it is likely that many important opportunities will be missed and frustration with the slow pace and poor yield of traditional development pathways will continue to escalate.

This commenter cannot agree with the Agency here.

The reality is that until and unless the medical products industry can be “convinced” to give priority to developing cures and preventative therapies or, *at a minimum*, to give the same weight to developing cures and preventive therapies as it is currently giving to developing “better treatments” at the expense of cures and preventive therapies, the consumers and the patients will continue to be increasingly less well-served by the medical products industry.

In the area of product development, “greater activity in a specific type of scientific research that is directed at modernizing the product development process” will make little, or no, progress in improving the process of developing medical products.

True progress in the product development area will require the developers to fully comply with all of the current applicable CGMP minimums.

In the development of drugs and drug products, the Agency urgently needs to require full compliance with all of the CGMP **minimums** governing incoming materials (*including, but not limited to, scientifically sound and appropriate identity as well as the scientifically sound and appropriate control of all of their critical physical and chemical characteristics*), processing controls (*including, but not limited to, the scientifically sound and appropriate assessment of sufficient batch-representative samples to permit the valid prediction of the outcomes of each significant manufacturing phase at a confidence level of not less than 95%*), in-process materials (*including, but not limited to, the valid assessment for uniformity, at a confidence level of not less than 95%, of sufficient batch-representative samples of each batch for all critical characteristics that may adversely affect the material or the product*), and products (*including, but not limited to, the scientifically sound and appropriate assessment of sufficient batch-representative samples for all of their critical characteristics using statistical quality control criteria for the assessment of the acceptability of each batch for release*).

In the area of devices, the Agency needs to require full compliance with all of the CGMP **minimums** set forth in **21 CFR Part 820, QUALITY SYSTEM REGULATION** in a manner that is sufficient to ensure that each medical device released is predicted at release (at a confidence level of not less than 99%) to meet all of its critical performance characteristics over its established usage lifetime.

Until and unless the preceding are implemented and the short cuts that today’s medical products industry is routinely taking (*e.g., the non-representative sample evaluation of an insufficient samples for only a few characteristics against inappropriate specifications and batch acceptance criteria*) are halted, and full CGMP compliance required, the industry will continue to experience unnecessary process development problems and late-stage product failures as well as the increasingly common post-approval product problems and failures that injure, maim, and kill some of those who take such medical products regardless of the “scientific research” “directed at modernizing the product development process” or the nature of “the highly pragmatic and targeted in its focus on issues such as standards, methods, clinical trial designs, and biomarkers.”

As long as the medical products industry is, *as it is today*, allowed to guess at the safety and efficacy of its new processes and products (based on the inadequate controls and specifications used, the insufficient number of non-

representative samples evaluated, or similar deficiencies that permeate today's process and product development activities where often, the samples evaluated either have no batch or population predictive power [when they are non-representative] or their population predictive power is severely limited because an insufficient number of population representative samples are evaluated using the knowingly deficient: **a)** specifications, **b)** sampling plans, **c)** standards, **d)** test methods, and/or **e)** acceptance criteria that today's medical products industry is permitted by the Agency to get away with using in place of the CGMP-compliant ones mandated by CGMP).

"Dealing with product development problems is the day-to-day work not only of clinical research and product developers, but also of FDA review scientists. The Agency frequently attempts to resolve problems identified during the review process. Extensive experience in evaluating and working to overcome hundreds of product development challenges and roadblocks has enabled FDA to intervene in a targeted manner, helping to reduce or remove specific obstacles in areas critical to public health. However, there are a host of additional opportunities where more progress is both necessary and possible."

While this commenter does not disagree with most of the Agency's statement, this commenter would characterize the magnitude of the "opportunities where more progress is both necessary and possible" as "some" rather than "a host."

"Due to the scope of the existing problems in product development and the expected surge in products resulting from investments in translational research, we believe that critical path research and standards programs should be high priority to help ensure that scientific innovations can be translated efficiently into public health benefits."

This commenter disagrees with the Agency's characterization of the reasons for the Agency's 180-degree about face here, from a slowdown "crisis" to an "expected surge in products."

However, this commenter does agree that there will be a "surge in products" submissions because, *as this commenter and others have noted*, there has been a recent surge in the number of pre-submission-related activities in the medical products industry and publications that presage such submission surges.

However, *until the industry changes its emphasis from "better" treatments* (that, in many cases, are, in the final analysis, mostly lucrative cash cows rather than intrinsically superior [e.g., Aleve]) *to condition prevention and cure*, this commenter sees little hope that most of these new medical products will truly provide "public health benefits" that even match their long-term public health costs.

Based on recent history (e.g., the Lyme disease vaccines and Baycol), some of these new medical products will: **a)** not benefit the public health,

but **b)** will provide: **i)** the medical and medical products industries with a new source of revenue as they treat those damaged and maimed by such new medical products, and **ii)** the legal industry with a new source of clients as the relatives of those killed and those maimed and injured seek civil redress for what, *based on the recent instances cited*, will be the knowing misconduct of those firms who seek and obtain approval for such products by minimizing and concealing the evidence of the risks while inflating the alleged “public health benefits” of such.

Obviously, the Agency is reducing its efforts in areas that protect the public health (e.g., failing to support and require CGMP compliance in the written “utterances” it publishes [even though so doing is at odds with the law] and redirecting its limited resources away from the bi-annual CGMP-compliance inspections [even though such CGMP inspections are mandated by statute], and marketbasket sampling and testing to ensure products do meet their standards) into, *as this document does*, areas that, *notwithstanding the Agency’s rhetoric*, principally benefit the medical products industry and not the overall health of the American public.

A public who, in general, is increasingly unable to afford, or have access to, the medical products industry’s current products much less their ever more costly new medical products that the industry is free to charge whatever it wants to and, through direct-to-the-consumer advertising and off-label-use promotion, to inflate their revenue streams from such as much as they can.

“These additional efforts should be targeted towards removing specific identified obstacles in development. Although there are numerous public and private groups with expertise to help develop solutions, we believe that FDA is ideally positioned to bring together the stakeholders to identify and address the most significant problems. We believe that efforts targeted at significant challenges and roadblocks have yielded important returns, and can have even greater public health benefits in the near future.”

For the numerous reasons previously stated, this commenter cannot accept the Agency’s rhetoric here.

Based on the Agency’s rhetoric and recent actions, where increasingly the “public” meetings it holds are only open to those who can afford the thousands of dollars needed to attend the conferences where the Agency, medical products industry, and industry-supported academia “publicly” meet to discuss these issues, the only stakeholders that the FDA wants to bring together “to identify and address the most significant problems” are the members of the industry that the Agency is supposed to regulate.

This commenter agrees with the Agency, “efforts targeted at significant challenges and roadblocks have yielded important returns” for the medical products industry – the industry’s revenues and profits have increased at more than twice the rate of inflation.

However, all that the majority of the public has received from these efforts is more expensive healthcare and less general access.

Though some have truly benefited; some have been injured, maimed and killed by the new products that these efforts helped provide.

Sadly, *at one level*, this entire document is another attempt by the Agency to justify its increasing support of the medical products industry at the expense of the public's health and programs that protect the public health by portraying the Agency's efforts as providing undefined "greater public health benefits in the near future."

"Without this investment ... frustration with the slow pace and poor yield of traditional development pathways will continue to escalate"

Other than the Agency's rhetoric, this commenter sees no proof and, *based on his knowledge and understanding of the situation for drugs*, does not think that the Agency's pronouncements and prognostications are any better than those of the average circus fortuneteller.

"The Orphan Products Grant Program

FDA's Orphan Products grant program provides an instructive example of a successful targeted intervention. This program provides up to three years of very modest funding (\$150,000-300,000 per annum) for clinical development costs of qualified products. Between 1989 and 2003, FDA approved 36 novel products (including 23 novel drugs) participating in this program. Thus orphan grant recipients have been an appreciable part of the 20 to 40 new drugs approved yearly during the last 14 years, despite the fact that industrial development of drugs for such limited uses is traditionally very hard to stimulate and only limited funding has been available.³² Recipients of orphan grants also benefit from advice and direction from FDA scientific reviewers on surmounting development obstacles. This program is widely viewed as a major success in assisting in development of treatments for rare diseases, at a very modest investment. FDA is conducting an internal review of how the successes of the Orphan Products development research might be applied to other kinds of critical path problems.

³² For comparison, FDA approved a total of 21 novel drugs in 2003.

FDA's Orphan Products grant program provides an instructive example of a successful targeted intervention"

This commenter does not agree with much of what the Agency has said here,

While recognizing the FDA views this program "as a major success in assisting in development of treatments for rare diseases," this commenter notes that, *as the Agency states*, this program has not provided cures and preventive therapies – while treatments are necessary, they should only be thought of

as stop-gap measures until a cure can be found and not, *as they are currently accepted to be*, lifelong palliatives.

Moreover, *given the industry's alleged "million dollar" costs for to bringing a single product to market*, it would seem that these "orphan" products only made it to market because the medical products industry believed that the profit to be made outweighed their costs and was more than happy to use FDA funds and personnel to assist them.

Similarly, *through this initiative*, the industry is seeking to get as much additional assistance from the FDA as it can convince the Agency to justify – knowing full well that every dollar redirected in this manner is one less dollar that the Agency has to use in regulating the industry's knowingly non-compliant conduct.

Thus, *though clothed in future benefits to the public health*, this initiative is an obvious industry-backed proposal to facilitate their marketing of better treatments while continuing to reduce the risks that their violative actions will be discovered – an obvious win-win situation for the industry and another losing proposition for the public.

As with the FAA, the FDA, *having been given responsibilities to speed new medical products to the market as well as to protect public health by the "Food and Drug Administration Modernization Act of 1997,"* has been, and is, increasingly becoming a federal agency that places the interests of those it is charged with regulating above the interests of the public that it is charged with protecting.

Until the FDA is held to account for: **a)** regulation-related publications that are plainly at odds with any applicable clear regulation (in violation of the Supreme Court's unanimous 1988 ruling in *Berkovitz v. USA*) and **b)** its knowing and willful failure, by allocating its resources into other areas as this initiative proposes) to even try to meet its statutory bi-annual inspection mandates (as set forth in the **Federal, Food, Drug, and Cosmetic Act**), the Agency will continue to engage in practices that are not only illegal but also practices that obviously are subverting the regulatory process (an action that, under **GDEA**, is in and of itself actionable).

Of course, such actions are supported by the medical products industry because the medical products industry is opposed to any regulation that does not directly benefit the industry's bottom line, including, but not limited to, the CGMP regulations that thwart the medical products industry's marketing of the substandard product batches and medical device items that many firms have been and are offering for sale today, based on the FDA Form 483s, Warning Letters, Seizures, Injunctions, Consent Decrees, Civil and Criminal Fines, and lawsuits both past and present.

"The Next Steps

The slowdown in new medical products reaching patients in recent years despite growing public and private investment in R&D and tremendous progress in the basic biomedical sciences illustrates that better biomedical ideas alone are not enough.”

As this commenter and others have stated, there has been no real “slowdown in new medical products reaching patients in recent years.”

As with any research-driven activity, the flow of new products occurs in waves and, at best, the current situation is but the trough of the next wave that even the Agency has admitted in this document they see coming, “Due to the scope of the existing problems in product development and **the expected surge in products** resulting from investments in translational research, we believe that critical path research and standards programs should be high priority to help ensure that scientific innovations can be translated efficiently into public health benefits” (**bolding emphasis added**).

“We must also ensure the successful movement of those ideas along the critical path of development, ultimately delivering reliable, safe, and effective treatments to patients at affordable prices. We must achieve breakthroughs in the way we get these treatments to patients and make them practical and efficient to develop and produce. This is an essential step in achieving more timely, affordable, and predictable access to therapies based on the latest biomedical insights — that so far are having little impact on patient care. If we do not work together to find fundamentally faster, more predictable, and less costly ways to turn good biomedical ideas into safe and effective treatments, the hoped-for benefits of the biomedical century may not come to pass, or may not be affordable.”

Again this commenter objects to the FDA’s attempting to abandon its regulatory role and, *under the false mantle of* “ultimately delivering reliable, safe, and effective treatments to patients at affordable prices,” blatantly supporting the industry that the FDA is supposed to be regulating.

The FDA does so at the expense of the health of the public that, *in all cases*, would be better served by cures and preventive therapies than by the “better” treatment that all know will only increase the cost of healthcare and reduce the affordability to the public.

The Agency’s initiative seems to support a treatment-driven healthcare system aimed at extracting the most money that it can for the benefit of the industries involved (medical products, medical-service providers, and healthcare insurers) with little, if any, real concern about: **a**) the long-term health of the public **or b**) the public’s ability to pay.

“Ensuring that the development pathway keeps pace with biomedicine is crucial to advancing the health of Americans. This must be a joint effort involving the academic research community, industry, and scientists at the FDA, and it must be launched soon to have a timely impact. In the months ahead:

- FDA will lead in the development of a national Critical Path Opportunities List intended to bring concrete focus to the tasks that lie ahead

- We will develop this list through extensive consultation with all public and private stakeholders.
- In addition, FDA will make internal changes to intensify its ability to surface crucial issues and to support high-priority critical path research efforts.

Since FDA is involved in setting standards for the development of new medical products, we must take proactive steps to use the best science to guide the development process and ensure that development standards are rigorous, efficient, and achieve maximum public health benefit.

We look forward to working with the scientific and product development communities to take advantage of this unprecedented opportunity to improve the health of the public and its access to affordable, innovative treatments.

FDA will lead in the development of a national Critical Path Opportunities List ... to bring concrete focus to the tasks that lie ahead”

After carefully reading the Agency’s remarks here and weighing what the FDA is saying against the FDA’s mandate to protect the public health and the realities in the healthcare marketplace, this commenter can only observe that, *rhetoric aside*, this document commits the Agency to a path that continues to abandon the FDA’s responsibility to protect the public health and safety in the medical products area and engaging in activities that support more and better new *treatments* that will be more costly. The Agency’s “critical path” treatment-centric initiative *seeks to advance new and costlier treatments at the expense of cures and preventive therapies* – therapies that would truly benefit public health and reduce overall healthcare costs – a course of action that, based on recent public industry comments on “**60 Minutes**” and elsewhere, the medical products industry is increasingly unwilling to support.

As any prudent person reviewing the medical products industry’s history recognizes, “better” treatments produce increased revenues that, Agency rhetoric aside, drive up healthcare costs and drive down healthcare availability

Having reviewed and, in some depth and with specificity, commented upon this background document that the Agency is using as its basis for creating Food and Drug Administration’s Docket No. 2004N-0181, “Critical path Initiative; Establishment of Docket” this commenter will proceed to address the requests for comment contained therein.

The published notice states:

“Critical path Initiative; Establishment of Docket

AGENCY: Food and Drug Administration, HHS. :

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is establishing a public docket to obtain input on activities that could reduce existing hurdles in medical product design and development. As described in a recently released Report, ‘Innovation/Stagnation: Challenge and Opportunity -on the Critical Path to New Medical Products,’ there is an urgent ‘need’ to modernize the product development toolkit, to make the development process more predictable and less costly. FDA is seeking input in identifying and prioritizing the most pressing medical product development problems, and the areas that provide the greatest opportunities for rapid improvement and public health benefits. To this end, we are establishing this open docket – to obtain input from industry, patients, academics investors, and all interested parties.

DATES: Submit written or electronic comments through July 30, 2004.

ADDRESSES: Submit written comments concerning this document to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville; MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Lisa Rovin, Office of the, Commissioner (HFP-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857-0001, 301-827-1443.

SUPPLEMENTARY INFORMATION

I. Background

On March 16, 2004, FDA released a report, ‘Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.’ (The full report is available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.) The report notes the recent slowdown in new medical products submitted for approval to FDA, and describes ways in which the product development process, the ‘critical path,’ could be modernized to make product development more predictable and less costly. According to Acting FDA Commissioner Lester Crawford, ‘A new focus on updating the tools currently used to assess the safety-and efficacy of new medical products will very likely bring tremendous public health benefits.’

Recent investments in basic medical research and translational research are intended to promote scientific discoveries and move some of them into medical testing. At that point, however, a potential medical product’s journey from concept to commercialization is far from complete. To produce a commercial medical product, developers must successfully negotiate a “critical path” to ascertain whether the potential drug, device, or biologic is effective and sufficiently safe for use, and how it, can be safely and reliably manufactured. Each of the three dimensions of the critical path—assessment of safety testing, proof of efficacy, and industrialization—presents its own set of scientific and technologic challenges, often unrelated to the science behind the mechanism of action of the product.

The ethics of human testing required (requires?) that there is a reasonable assurance of safety before people are exposed in clinical trials. The tools used to predict preclinical safety (e.g., animal toxicology) are time consuming and cumbersome. In some cases, particularly for assessment of products based on recent innovative science, entirely new tools must be developed: There is an urgent need for new biomarkers for evaluating safety during human trials.

Demonstrating the medical effectiveness of a product is one of the most difficult challenges in product development. Even identifying the best way to assess whether a product is effective (what symptoms or physiologic indicators should be followed and for how long) can present significant unknowns.

Product development companies must figure out how to manufacture large amounts of the product reliably. Turning a laboratory prototype into a mass produced medical product requires solutions to problems in physical design, characterization, manufacturing scaleup and quality control. These problems can be rate-limiting for new technologies, which are frequently more complex than traditional products.

Because of its unique vantage point, FDA can work with outside experts in companies and the academic community to coordinate, develop and/or disseminate solutions to critical path problems, to improve the efficiency of product development industrywide.

The first step is to identify and prioritize the most pressing medical product development problems, and the areas that provide the greatest opportunities for rapid improvement and public health benefits. It is critical that we enlist all relevant stakeholders in the effort. Such a national ‘Critical Path Opportunities List’ is intended to bring concrete focus to tasks (whether best undertaken by industry, academia, FDA, by others, or jointly) that can modernize the critical path.

For additional information, you may visit FDA’s critical path home page at <http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.fda.gov/oc/initiatives/criticalpath>.

II. Request for Comments

We are seeking input on identification of the most pressing scientific and/or technical hurdles causing major delays and other problems in the drug, device, and/or biologic development process, as well as proposed approaches to their solution. For each critical path hurdle, we are particularly interested in receiving the following information. Please note that the material submitted to this docket will be publicly available.

1. Hurdle Identification. Please describe the product development issue, the nature of the evaluation tool that is out-of-date or absent, how this problem hinders product development, and how a solution should improve the product development process. Please be as specific as possible.

2. Please rank each hurdle identified in Question 1, above, in priority order according to which hurdles create the most severe product development problems. That is, which problems present the greatest opportunity for improving product

development processes? Our goal is to identify those aspects of product development that would most benefit from new evaluation tools.

3. For each problem identified, please indicate the "type of drug", biologic, or device to which the hurdle applies.

4. For each problem identified, if a solution would facilitate the development of drugs, biologics, and/or devices for a particular disease or categories of disease, please indicate which diseases would be-affected?

5. Nature of the Solution. For each problem identified, please describe the evaluation tool that would solve the problem and the work necessary to create and implement the tool/solution. For example; would a solution come from scientific research to develop a new assay or validate a new endpoint? If the solution involves biomedical research, please specify the necessary research project or problem. Would a tool be developed through data mining or computer modeling? Would the right tool be a new FDA guidance or industry standard? If work on a solution is underway, what steps remain? Are there other innovative solutions that could be explored?

6. For each solution identified, please indicate which could be accomplished quickly, in less than 24 months, and which require a long term approach?

7. For each problem identified, what role should FDA play and what role should be played by others? Should FDA play a convening role, bringing the relevant parties together to discuss an approach or solution? If so, who else should participate. Should FDA coordinate scientific research, the results of which would be publicly available? We are seeking Input on ways to target FDA scientific and collaborative activities to help industry bring more safe and effective medical products to us for review.

8. What factors should guide FDA in setting priorities among the hurdles and solutions identified?

III. Submission of Comments

Interested persons may submit written or electronic comments to the Division of Dockets' Management (see **ADDRESSES**). Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. You can also review received comments on the Internet at <http://www.fda.gov/ohrms/dockets/dockets/docket.htm>."

Commenter's Proposed "Critical Path" Initiatives

In response to the preceding requests and after a careful review of the FDA's basis document, this commenter submits the following "critical path" initiatives, *in order of importance*, that are needed to bring the medical products industry into full compliance with CGMP in a manner that ensures that said medical products are:

- Not adulterated *as that term is defined in 21 U.S.C. 351(a)*,
- Safe and effective,
- Of the quality they are purported or represented to have, **and**
- Preferentially, cures and preventive therapies rather than “better” treatments:

**“Critical Path” Initiative 1:
Enforce CGMP Compliance That Is Ensures:
Controls, Including Specifications And Acceptance Criteria, Are:**

- ❖ **Scientifically Sound And**
- ❖ **Appropriate**

Criticality: Severe

Impact: Universal: All Medical Products, Developmental, New and Existing

Timeframe: Immediate: Required by law since 1979

Commencing during the initial development of each medical product and thereafter, this three-fold initiative should:

1. **Require all medical product firms to provided detailed written proof that:**
 - a. **For drugs**, *including drug components, drug products and biologicals*, the specifications (including batch or lot acceptance criteria), standards, sampling plans, and test procedures are:
 - i. Designed to assure that each lot or batch of components, drug product containers, closures, in-process materials, labeling, and products are predicted, **at a confidence level of not less than 95%**, to meet, *or exceed*, all of the predetermined critical characteristics required “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”, **and**
 - ii. *Based on the evaluation of sufficient batch representative samples*, adequate to ensure, **at a confidence level of not less than 95%**, that each lot or batch inspected, *not just the samples tested*, does meet, *or does not meet*, the acceptance criteria established for said medical product.
 - b. **For devices**, the specifications (including device acceptance criteria), standards, inspections, and test procedures are:
 - i. Designed to assure that each device component is suitable for its intended use and each device accepted for release is safe and effective, and is predicted, **at a confidence level of not less than 95%**, to meet, *or exceed*, all of its predetermined critical characteristics, **and**

- ii. Based on the evaluation of sufficient samples to assure that the results obtained from the inspection of each device inspected ensure, **at a confidence level of not less than 95%**, that each device, *not just the samples inspected and tested*, does meet, or does not meet, the *acceptance criteria* established for said device.
2. **Require all medical product firms to provide detailed written proof that:**
- a. All of their specifications are based on the proper application of statistics to *population representative samples* from each batch or lot, *for drugs and drug products*, and, *for devices*, each device, lot, batch, or production run, as appropriate,
 - b. The firms have *statistically sound and appropriate specifications* and *acceptance criteria* for all of the critical characteristics of all incoming materials, in-process or in-production items including labeling, and all product items, **and**
 - c. The firms use recognized *statistical quality control science* and, *wherever such exist*, recognized consensus standards in the taking, and testing or examination, of appropriate *population-representative samples* from each lot, batch, or production run for their product- or process-critical characteristics during each significant phase of manufacturing including acceptance for release.
3. **Require all medical product firms to:**
- a. Compute and report: **i) the confidence level and ii) result uncertainty** (overall variance, testing, tester, and test procedure, [and data range] and the number of data values used to compute each result) associated with any **result value** generated by any evaluation of any sample, sample set or subjects. [Note: Were the valid **confidence level** and **result uncertainty** for each **result value to be reported**, any reviewer thereof would, at a glance, be able to easily comprehend the general import of the result values reported. From this commenter’s viewpoint, much of the analytical “confusion” that is present exists because, *to obscure the result values*, the medical products industry reports only the average values found – that this is a problem can be illustrated by the following simple examples, a result of a “99%” can be the average of “79% and “119%” or of “98%” and “100%,” and the test used can have an overall uncertainty of 0.5 % or 5%, and the level of confidence can be 5% or 95% – lacking ready access to this information, all the reviewer sees is a result of “99%”– little wonder that providing such values often leads to “unpredicted” problems, and failures.], **and**
 - b. Suitably incorporate all of those computed values into the computation of the statistical quality control estimate of the acceptability, as *appropriate*, of the lot or batch (for drugs) and the individual unit, lot, batch, or production run for devices.

Were the Agency to fully enforce the specific CGMP minimums outlined above from the first time that a developmental medical product was being

manufactured for any experiment in which a “new medical development” candidate was to be given to, or used in or on humans, then many of the subsequent experiment failures and product problems would be identified sooner and, *because a minimum confidence level of 95% would be required*, the predictive reliability of experiment outcomes would also increase.

In this commenter’s personal experience, this commenter has seen both newly approved and other medical products (drugs and drug products) that the firm having the approval repeatedly had problems with, or had to abandon because:

1. The development process failed to include rigorous statistics-based controls on the characteristics of one or more of the components, *including, but not limited to, the API*, and, *because of subsequent changes in or variation in one or more said components*, the approved process and the product it produced were found to be unusable during: **a)** initial process validation, **b)** a subsequent campaign when the component supplied met its specifications (that failed to characterize and appropriately control component variability) but the batches made from said component failed to meet the firm’s in-process and/or release specifications and/or acceptance criteria, **c)** a complaint investigation, **or d)** an FDA-market-basket or customer-initiated evaluation.
2. The developmental process and the filed submission failed to take and evaluate a sufficient number of *batch representative samples* or implement *scientifically sound, and appropriate CGMP-compliant controls* that, *during a product-problem investigations*, led the firm to realize that the approved process failed to make drug product batches that complied with **21 CFR 211.101(a)** – forcing the firm to cease manufacturing that product.
3. The drug-product manufacturing firm failed to have adequate contractual controls on changes to the manufacturing process of the API and, *after the API manufacturer made “simple” production changes* (e.g., in crystallizer scale, or solvent addition order), accepted lots of an API that: **a)** could no longer be uniformly distributed in the final blend using the approved manufacturing practice, **or b)** altered the drug-products “dissolution” characteristics to the point that the batches were not assured of meeting either their release or post-release specifications).

In addition, this commenter has seen numerous instances where considerable product development effort was expended based on the results from a few non-population-representative experiments or tests and, *based on subsequent test results or experimental findings*, the product development had to be abandoned or, *because of the components used to make the initial batches upon which the development and initial filings*, the manufacture of uniform batches that truly exhibited the same performance characteristics as the developmental batches was either problematic or, *because the manufacturer of one of the critical formulation components had difficulty producing batches that could be used to manufacture acceptable product*, adversely affected or restricted (e.g., an

extended-release product that used a special “Methocel” whose characteristics were so “special” that: **a)** Dow had trouble identifying lots that might be acceptable, **b)** the firm had to manufacture and test trial batches of pre-shipment samples from each candidate to find that, *on average*, less than 25% of the Dow-selected candidates were acceptable, **c)** an occasional batch of the drug-product (made from some accepted special “Methocel” lots) was projected to have a slight risk of post-release compliance problems, **and d)**, *because of that component’s irregular availability*, the manufacturer not only had difficulty filling customer demand at times but also could not actively seek to expand its market).

As an adjunct to this initiative, the developers need to ensure that the lots of components they use in development are from the most probable portion of the component manufacturer’s product distribution (the “1-sigma” lots that comprise more than two-thirds of the batches produced). [Note: As a corollary, only component manufacturers who can and do provide such assurances should be used as suppliers either in development or subsequently unless the supplier in question is the sole source and, *because of that fraction of said vendor’s production that is already so committed*, the vendor can only assure that the lots furnished are in the “2-sigma” envelope – vendors that cannot, or are unwilling to, provide such certifications should not be used in development (or subsequently) because they cannot ensure that all batches supplied will be essentially the same as those used in development and manufacturing.]

**“Critical Path” Initiative 2:
Implement A Journey-Based Approach To “Validation” That**
❖ **Begins In Pre-Clinical Development And**
❖ **Continues Throughout The Medical Product’s Lifetime**

Criticality: Severe
Impact: Universal: All Medical Products, Developmental, New and Existing
Timeframe: Immediate: Required by law since 1979

Commencing during the initial development of each medical product and thereafter, this initiative should require a manufacturer to adopt an integrated “water fountain based” approach to a product-based “validation” of the process steps used to manufacture each medical product unit.

To facilitate the proposed lifelong-journey-based approach to validation, this commenter offers, beginning on the following page, a suggested self-consistent terminology set to address the proposed integrated “validation” of a medical product (“new” or existing) as well as a “water fountain” model approach to switching from a current “Validation” stage to the appropriate prior stage when difficulties arise in the current “Validation” stage.

“Self-consistent ‘Validation’ Terminology

<p>NOTA BENE: <i>Though the following is the intellectual property of FAME Systems and this commenter, a license for use thereof is freely granted to all who wish to use the concepts and ideas contained therein, <u>provided</u> the concepts and ideas presented</i></p>
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therein are NOT taken out of context and provided written credit is given to the source.

Today, the topic of ‘validation’ has matured to the point that a set of self-consistent terms is needed. [Note: Since the FDA recognizes that validation is a journey (in the preamble to the proposed changes to the CGMP regulations as well as in the FDA’s **CPG 7132c.08** (effective March 12, 2004), titled ‘**Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval**,’ that addresses the Agency’s current views on process validation requirements in a manner that clearly agrees with the in-process CGMP regulations’ ‘each batch,’ journey view as set forth in **21 CFR 211.110(a)** and states (with *emphases added by this commenter*) in Sec 490:100, ‘**Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110)**, and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. *A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase.*’ Since this journey must span the lifetime (“beginning from the process development phase and continuing through the commercial production phase”) of whatever drug-manufacturing process (**21 CFR 211.110**) or device manufacturing process (**21 CFR 820.75**) the firm is ‘validating,’ the term ‘revalidation’ is not consistent and should be removed from the pharmaceutical industry’s lexicon. Provided the term ‘revalidation’ is removed then there is also no basis for the equally inconsistent term ‘re-qualification.’]

Recognizing that **21 CFR 820**, as revised in 1997, also rightly starts ‘validation’ when the design of the process is initiated, the terms used to describe the various phases of validation must begin with DESIGN (or, as it is usually labeled for drugs, DEVELOPMENT).

Most who address any facet of validation also recognize that, after DESIGN (or DEVELOPMENT), the process or whatever entity is being validated must be BUILT (although the misnomer that is commonly used for the next phase is INSTALLED), and OPERATED (commissioned) using test feeds, controls and checks to assure that the installed hardware and software do operate as they were designed.

When acceptable operation has been achieved, the developing firm must next intensively EVALUATE the performance of the process (or whatever the entity is) to establish that it can meet its predetermined specifications and other expectations, or that it otherwise consistently and reliably performs as expected.

This is point at which pharmaceutical industry and the Agency seemingly abandon the concept of ‘validation’ as a journey.

What should the next phase of the ongoing validation journey encompass?

If it truly is a journey, then some umbrella term is needed that encompasses all phases of the journey beyond the stage at which performance is established by intensified EVALUATION.

Instead, we have change control, annual review, equipment maintenance, deviation control, investigation, etc.

For this phase, the root term proposed is MAINTAIN.

Finally, when we get to the stage where, *for whatever reasons*, the process, or *whatever*, is to stop being used or be replaced (decommissioning), few have any pre-planned approach to address such events.

For this phase, the root term proposed is CLOSE.

To be complete, the proposed self-consistent terminology set must address ‘legacy’ systems that exist and are functioning, but, *for whatever reason*, have not yet been placed within a ‘validation’ umbrella.

Moreover, the self-consistent set must incorporate explicit terminology that covers the existing entities from their beginning to the present moment.

Finally, because validation is a journey and not a destination, the firm should not state that ‘we have validated ...’ but rather state that ‘we are validating ...’

Based on the preceding, the well-defined terms ‘**Qualify**’ and ‘**Verify**’ lend themselves to processes and other entities that are, *respectively*, **a)** covered from inception, **or b)** existent, functioning, or in use before the firm has, for whatever reasons, initiated ‘validation.’

With the preceding in mind, let us consider using self-consistent terminology set that treats:

- a) ‘**Validation**’ as a journey and
- b) ‘**Qualification**’ and ‘**Verification**’ as the means by which milestones are met and/or the continuing conformance to the path established is confirmed.

Terminology Framework

Based on the preceding, let us define ‘**Validation**’ as a six-phase journey that starts with the basis label set:

- ❖ **Design** (or **Develop**).
- ❖ **Build** (currently, referred to as ‘Install’).
- ❖ **Operate**.
- ❖ **Evaluate** (currently, referred to as ‘Perform’).
- ❖ **Maintain**.
- ❖ **Close**.

To address both new and legacy entities, let us add the terms ‘**Qualification**’ and ‘**Verification**’ to our basis set to produce the following eighteen-term set:

- ❖ **Design/Development**.
 - **Design/Development Verification** (“**DV**”).
 - **Design/Development Qualification** (“**DQ**”).
- ❖ **Build** (currently, implicitly "Install").
 - **Build Verification** (currently, Installation Verification) (**BV** [**IV**])).
 - **Build Qualification** (currently, Installation Qualification) (**BQ** [**IQ**])).
- ❖ **Operate**.
 - **Operation Verification** (**OV**).
 - **Operation Qualification** (**OQ**).
- ❖ **Evaluate** (currently, implicitly "Perform").

- **Evaluation Verification** (currently, Performance Verification) (**EV [PV]**).
- **Evaluation Qualification** (currently, Performance Qualification) (**EQ [PQ]**).
- ❖ **Maintain** (currently, not widely used).
 - **Maintenance Verification (MV)**. [Note: To be self-consistent, **MV** must become **MQ** after the Validation of an existing entity “passes” the preceding phases (**DV, BV, and OV**).]
 - **Maintenance Qualification (MQ)**.
- ❖ **Close** (currently, not widely used).
 - **Closure Verification (CV)** [Note: This term added to maintain consistency but would only be appropriate for the retrospective review of a superseded entity. Moreover, because it deals with a “dead” system, it does NOT, *a priori*, require that the preceding “Validation” phases be addressed and completed.]
 - **Closure Qualification (CQ)**.

Further, because this terminology set is designed to address ‘living’ systems, let us specifically provide that the validation activity is free to revert to any prior phase should outcomes dictate a need for such action, **provided** such reversions are:

- a) Pre-planned **and**
- b) Properly controlled.

To this end, let us agree that the terms ‘**Validation Protocol**’ and ‘**Validation Plan**’ are synonymous, and refer to a document that outlines and defines the overall connections and relationships among all of the terms in the set as well as the responsibilities and authorities of all those who are, in any manner, a part of the validation of the entity that a given ‘**Validation Plan**’ addresses.

Thus, one can have a ‘**Validation Plan**’ for a site, a building, a service, a process, an equipment system, a piece of equipment, a method or procedure, a work instruction, software, or, *for that matter*, a documentation system or a single document.

Similarly, the generally accepted term, ‘**Validation Master Plan**’ is the overall plan for some set of components that are to be, or are being, considered as a whole.

In general, such master plans refer to processes, sites, and complicated systems.

The level of detail and complexity that a firm chooses to cover in any plan will depend on the policies set by each FDA-regulated firm.

In any case, *as with any mature concept*, a self-consistent set of terms, *such as the set proposed*, is needed.

Moreover, that terminology set, *as the one proposed is*, should be usable by all of the areas regulated by the FDA, drug, drug product, device, diagnostic product, cosmetic product, food, nutritional product, biological product, biotech product, and radiological product as well as the support areas of special interest to the FDA (e-records, e-signatures, hardware, software, firmware, methods, and processes.”

Based on this commenter’s preceding approach that provides: a) a self-consistent terminology set for use in addressing ‘validation’ and b) a built-in flexibility that explicitly permits a “for cause” reversion from the medical product’s current stage in its “validation journey” to any appropriate prior stage, the “water fountain” model, where the output from any stage is allowed to “flow” down to

whatever prior level that it needs to from development upwards, best describes flexibility that should be built into any CGMP-compliant lifelong-journey-based “Validation Plan” generated for any medical product.

Moreover, because each “**Validation Plan**” is a living document, the standard operating procedure (SOP) used to generate and modify each such should explicitly incorporate a flexible framework approach that starts with the appropriate six (6) basis tiers and explicitly permits each tier to be: **a)** fleshed out and **b)** modified in a manner consistent with the current history of the medical product covered by said plan.

Based on this commenter’s experience, the medical products industry, as a whole, not only fails to be quality and statistical control proactive (a shortcoming that **Initiative 1** addresses), but also fails to use a CGMP-compliant integrated medical-product lifetime planning approach (“validation”) for its products.

Coupled with the failure to use *scientifically sound and appropriate* population-representative experiments and samples’ inspections in development and ongoing process and production activities, these failures significantly contribute to many, if not most, of the problems that the Agency incorrectly attributes to deficiencies in the existing tools available to the medical products industry.

**“Critical Path” Initiative 3:
Implement The Use of Analytical Evaluation Procedures
Appropriate To Assessing Variable Factor Uniformity And Identity**

Criticality: Severe

Impact: **Universal:** All Medical Products, Developmental, New and Existing –
Mostly for Drugs and Drug Products

Timeframe: **Immediate:** **Required by law since 1979 for drugs**

In general, the Agency should proscribe the use of any and all *United States Pharmacopeia* (USP) test methods, and specifications for the evaluation of incoming and in-process materials at any stage in the manufacturing process, *including product acceptance for release for distribution*, unless the firm can prove that such are:

- a. Scientifically sound and appropriate,
- b. Statistically valid,
- c. Measures of material identity (not the USP’s IDENTIFICATION tests) or material uniformity, **and**
- d. Found, *under actual conditions of use*, to have an inaccuracy of on the order of not more than 2% relative and an overall testing (testing, tester, and method) variance of not more than 6%² (precision).

**Analytical Evaluation Methods For
Uniformity Assessment And Acceptability**

In place of the USP-type probable “class membership” procedures, the Agency should require that the test procedures used from the start of pre-clinical product release through product release should be focused on rapidly determining the identity, uniformity, and population acceptability of all materials and products.

Therefore, for variable factor level evaluations, this commenter would strongly recommend that, *instead of using the more inaccurate and imprecise hyphenated HPLC-detector methods that the USP favors* (based on the supposed selectivity that the HPLC separation provides even though, under USP-type separation conditions, the systems provide, at best, limited component resolution), firms would be better served by using today’s computerized component-deconvolution-software-equipped rapid-scan spectrophotometric detectors (e.g., UV, Visible, NIR, IR, Fluorescence, Raman) that have more sensitivity, accuracy, precision, and a much wider linear dynamic range than the typical scaled-down HPLC detectors typically used.

In addition, properly developed methods using such separationless direct measurement systems provide a much higher sample throughput (typically, between 5X and 20X) and significantly lower sample evaluation uncertainties than their HPLC counterparts.

Were the industry to adopt the use of such procedures, then:

- ❖ Much of the cost barrier (time and test) that the industry points to in an attempt to justify not properly testing a *population-representative* set of *samples* (as required by CGMP) be eliminated or greatly reduced,
- ❖ The time to test the requisite CGMP-minimum number of *population representative samples* would be significantly less than the current HPLC methods used to test an inadequate number of non-representative samples, **and**
- ❖ The accuracy and precision of the results obtained should, in almost all cases, be less than that introduced by the current HPLC methods.

[**Note:** This commenter would also recommend that the many other classical analytical techniques used should be updated to the most modern procedures that furnish the highest precision, acceptable accuracy, and the highest throughput.]

Analytical Methods For Physical Properties Assessment And Acceptability

Mostly for drugs and drug products, *in place of the limited, or non-existent, USP-type procedures for physical properties*, the Agency needs to require the industry to:

1. Determine which of the physical properties of each component affect the formulation (the “*critical physical characteristics*”),
2. Take and inspect batch-representative samples of sufficient size to accurately reflect the uniformity of each of the *critical physical characteristics* of each component that is required to be tested,
3. Initially use the results obtained to define *scientifically sound and appropriate, population-representative specifications and acceptance criteria* for each material, **and**

4. Use those scientifically sound sampling plans, test procedures, specifications, and acceptance criteria to determine the “physical properties” acceptability of each shipment of each lot of each component as required by the applicable CGMP regulations.

Further, *since, for solids and some semi-solid liquids, shipment may, and often does, change the distribution of the materials within the shipping containers*, the Agency should require that the firms either:

- Establish that worst-case shipping conditions do not affect the physical-properties distribution in each component used **or**,
- *Failing that*, sample and evaluate *lot-shipment-representative samples* of sufficient size for all of their *critical physical properties* and only accept lot-shipments where the *representative samples* evaluated meet all of their *critical physical properties* as well as their identity, and chemical properties.

[**Note:** As an adjunct to this the Agency should require each firm to submit the component criteria sections of all component contracts in the application to ensure that the submitter has the requisite contractual controls over the components purchased – these submissions should be required initially and whenever a firm proposes to change the source of a component or to add another supplier.]

This commenter has seen numerous examples where the medical products manufacturer’s failure to have such contractual acceptance controls has led the manufacturer to accept and use component lot-shipments that directly contributed to subsequent development, initial-validation (process-conformance-assessment) and/or routine-production problems and failures.

For example, in one “product development” case, the API manufacturer made a “minor” process change that slightly altered the crystallization solvent mixture to include a low level of acetone (done to “increase” the rate of crystal formation) and, *unknown to the API manufacturer*, this “minor” change significantly altered the surface-area-to-volume ratio of the crystals produced even though the apparent crystal shape and size distribution were not significantly altered.

Regrettably, the product developer’s specifications for the API failed to have a *scientifically sound and appropriate specification or test* for either: **a)** surface-area-to-volume ratio **or b)** intrinsic dissolution

Sadly, the batch of candidate “immediate release” product produced from that API lot had a drastically reduced release rate for the active to the point that it was unsuitable for use as an “immediate release” medical product,

Moreover, *when asked to revert to the prior* crystallization procedure, the API supplier found that it was “unable” to again produce “crystalline” API whose intrinsic dissolution matched that of the initial pre-change API batches – which, in turn, caused the drug-product developer to have to micronize the API and significantly change the formulation (to include a release accelerant) and the manufacturing process (from: **a)** direct blending to form the API-containing “pre-blend” that was mixed with a diluent and colorant to generate the “final blend” to: **b)** the generation of a suitable wet-granulated, dried, milled, and mixed “pre-blend”

that was then mixed with a release promoter, a diluent, and the colorant to form the final blend) for that drug product.

In another instance, post-approval “manufacturing” problems were traced to the failure of the firm to establish and have adequate controls on the physical properties (e.g., viscosity, density, polymer distribution, refractive index) on the critical characteristics of the release-control polymer used in the formulation – again a lack of controls, much less adequate controls, on the “critical physical properties” of a component led to post-approval manufacturing difficulties.

In a third example, the firm failed to have any controls on the “flow” properties of the API (though, in this case, the firm did have scientifically sound and *appropriate* “density,” “particle size distribution,” and “crystallinity” controls).

About three (3) years after product approval, the firm received several lot-shipments of that API that passed all of the firm’s “identity” and “physical and chemical property” controls, but were noted not to “flow” like previous lot-shipments.

The firm’s management directed that the lots be approved for use since they met all of the firm’s acceptance criteria and passed the USP’s tests.

Based on the results of a few non-representative drug product samples’ meeting the USP specifications for the drug product, the firm’s quality control unit (QCU) released the batches for distribution.

Subsequently, the FDA, in a market-basket survey found that the portions of the batches they sampled were adulterated (as per **21 U.S.C. 351(a)(2)(B)**) based on the USP test results obtained, and issued orders seizing not only all released batches but also all of the firm’s released API lots and in-process batches.

The Agency deemed the problem so severe that the firm was forced to agree to: **a)** cease manufacturing this drug product **as well as b)** give up the firm’s approval for all strengths of that drug product.

In a fourth example, the firm failed to test *lot-shipment-representative samples* for each component (the firm, as many do, used a CGMP-violative “1 + the integer of the square root of the number of containers” sampling plan) and release a batch of an excipient that (as a subsequent investigation found) that had “filth” and “oily metal particles” in some of the containers that were not sampled.

Because of the manner in which the firm added this component to the batch, the manufacturing process used, and the subsequent in-process and release testing performed, no recorded evidence of this problem was found until, after release, the firm received a complaint sample from a patient who, having been instructed to break the tablets in half and take half a tablet by the patient’s physician, found contamination in the tablet that the patient broke.

Using the firm’s retain sample and the three lot-number-identified tablets returned by the patient, an investigation into the source of the problem found that the contaminants were “filth” and/or “oily metal particles.”

A forensic-type examination of the particulate “filth” found inside of both the complaint sample and some of the retain tablets examined that its core was one particular excipient.

Though all batches containing the same lot of that component were recalled and a sampling of the remaining containers of the current lots of that component found that there was similar contamination in the bottom thirds of some containers, the drug-product manufacturer’s management elected to “request” the supplier to increase its release inspections but refused to allow the QCU to change the sampling plan for that component to “Top/Middle/Bottom” (“T/M/B”) from each container – management would only agree to change the sampling plan to the “Bottom” of twice the usual number of containers – though, given the failure, the QCU felt that the sampling should revert to “T/M/B” for each container and continue to be “T/M/B” until at least the lots in the next five (5) shipments were examined and found to be free of contamination, uniform, and meet all requirements.

Again, these “*critical path*” problems did not arise from the lack of some “tool” but rather, *as is usually the case*, from the failure of the developing firm to have and use *scientifically sound* and *appropriate* controls on the physical properties of the components they used as required by the applicable CGMP regulations.

Analytical Methods For Identity Assessment And Acceptability

In place of the USP-type “IDENTIFICATION” procedures, the drug-product CGMP requires the manufacturer to develop and use *scientifically sound* and *appropriate* material identity tests that are applied to *lot-shipment-representative samples* for all components, and: **a)** if specific identity tests exist **or b)** when the accept on supplier’s “report of analysis” option is selected, the identity test used for **Case “a)”** should be a specific identity test when such exist (**21 CFR 211.84(d)(1)**) or, for **Case “b),”** the identity test used must be a “specific identity” test (**21 CFR 211.84(d)(2)**).

Regrettably, the Agency continues to allow manufacturers to get away with the blatantly non-CGMP-compliant practice of using the USP’s “IDENTIFICATION” tests in lieu of the CGMP-required test “to verify the identity of each component” when the receiving manufacturer performs full evaluation “for conformity with all appropriate written specifications for purity, strength, and quality” on *lot-shipment-representative samples* from *each lot-shipment* (**21 CFR 211.84(d)(1)**) or, when said firm uses the supplier’s “report of analysis” in “lieu of such testing by the manufacturer,” a “specific identity test” on said *lot-shipment-representative samples* from each lot (**21 CFR 211.84(d)(2)**). [Note: The Agency even permits the developing manufacturer to use the “report of analysis” option set forth in **21 CFR 211.84(d)(2)** when the supplier’s “report of analysis” fails to provide the requisite specifications or report value for component “purity” – wrongly equating the uncertain USP-like “Assay” values the suppliers typically provide to the “purity” values required.]

In some cases, component lots, including API lots, may be accepted by the manufacturer even though the material in the lots is not truly the material that the labeling claims or purports it to be.

The worst-case example of this that this commenter personally knows of is the API named Sucralfate where:

1. Even the USP and the FDA both know that the USP monograph cannot identify the bioactive “drug” when the API supplier manufactures an isomeric “aluminum sucrose octasulfate” polymeric material because the **only** analytical test that can identify the structurally correct isomeric mixed polymer, *the isomeric form in which the Sulfate’s oxygen atoms in the Sucrose Sulfate moieties are coordinated to the Aluminum atoms*, is solid-state ¹⁹Al-NMR – an identity test that the USP refused to add to the monograph because that test was “too expensive.”
2. Based on: **a)** the clinical trials for the generic conducted by Mylan and Biocraft Laboratories, Inc. (now a part of Teva) **and b)** solid-state ¹⁹Al-NMR testing on all of the available putative “Sucralfate” source materials, the innovator’s Carafate tablets, and the generic products approved in Europe in 1989, the then-available API materials, *except from the API from one Chinese source*, and all of the then-available generic drug products failed to have the same solid-state structure as the innovator’s Carafate, **and**
3. The Mylan clinical trial for their “drug product” candidate: **a)** used a “Sucralfate” from a Japanese source that did not have the same solid-state coordination structure as Carafate, **and b)** failed to demonstrate the any clinical efficacy. [Note: By contrast, the Biocraft clinical trial: **a)** used a “Sucralfate” that was structurally equivalent to the innovator’s Carafate **and b)** was found to be clinically equivalent to Carafate. Unfortunately, the senior management of Biocraft was unwilling to press the USP to amend the USP monograph for Sucralfate to require a solid-state ¹⁹Al-NMR specific identity test that could identify the correct isomeric structure or, *because of cost*, to submit this “specific identity” test in the firm’s filings for the Sucralfate drug product even though said management knew that omitting this identity test would risk the firm’s accepting material lots that were ineffective because the material in the lots had a solid-state structure that was different from that of the API. In the early 1990’s, when this commenter brought this matter to officials in the USP and the FDA, neither group was willing to address it.]

Again, the “**critical path**” problem is not the lack of the requisite analytical tool, but: **a)** the unwillingness of the developing firm to routinely use the tool because of the cost **and b)** the refusal of both the USP and the FDA to require the use of this tool (solid-state ¹⁹Al-NMR) even though it is obvious that the use of this tool is required to establish that a material purporting or represented to be the drug Sucralfate really is: **i)** Sucralfate, **or ii)** a medically useless related structure. [Note: Since all of the sample workups that “dissolve” these polymeric organometallic materials destroy the coordination complex by splitting it into a hydrated Aluminum cationic species and a set of sucrose sulfate anionic species (principally, sucrose octasulfate and sucrose heptasulfate with traces of the sucrose hexasulfate in some cases).]

Further, *because of the Agency's failure to enforce the clear CGMP requirements with respect to component identity*, developmental and post-approval problems may and do arise from the manufacturers' unchecked knowing failure to develop and use a *scientifically sound and appropriate* "specific identity test" for the assessment of the identity of *lot-shipment-representative samples* of each drug-product component as the CGMP regulations suggest in **21 CFR 211.84(d)(1)** or clearly require in **21 CFR 211.84(d)(2)**.

This CGMP non-compliance gives rise to:

- a. The reality that, *without the manufacturer's even "knowing" that there is a problem*, a component may not be the component that the formulation specifies **and**
- b. The manufacturer's knowing non-compliance with this clear CGMP minimum results in drug products that may or do: **a) fail to help or b), in some cases, injure the recipients of such adulterated drug product batches.**

In development, such problem batches may cause the developer to abandon a potential valuable therapeutic drug, or, worse, proceed to develop a product that will found to be a problem after approval *when the nature of the component changes*, but, *because the firm performs no identity, or specific identity, inspection*, a subsequent accepted lot of a component is a material other than the material that it is represented to be. **[Note:** In some cases, where the then current USP or NF Monograph does not differentiate between: **a) materials having benign impurities and b) like materials having toxic impurities**, this problem has seriously injured, or been lethal to, those who received drug products made from accepted components in the later category (for example, oligomeric liquids, semi-solids and solids made from the polymerization of toxic starting material monomers where the purification process used fails to remove the toxic starting materials have had such problems – of course, after each such **discovered** incident in which the public is harmed and people die, the USP does correct that USP or NF Monograph).]

**"Critical Path" Initiative 4:
Require Those Who Conduct "CGMP" Sample Evaluations To Conduct
Them In Compliance With The Requirements Set Forth In ANSI/ISO 17025-
1999**

Criticality: Severe
Impact: Universal: All Medical Products, Developmental, New and Existing
Timeframe: Immediate

Introduction

In today's sample evaluation environment there exists a recognized minimum consensus standard that outlines, in some detail, a system that, *at a minimum*, all CGMP-regulated firms should be using whenever they evaluate a sample or require in their contracts when they contract with an outside firm for their samples to be evaluated.

That consensus standard is **ANSI/ISO 17025**, “General Requirements for the Competence of Testing and Calibration Laboratories.”

Though this standard uses the word “laboratories” in its title, it applies to all environments in which samples are evaluated or calibrations of equipment and reference standards are made, including the at-line, in-line, and on-line alternatives proposed in the Agency’s industry-backed “process analytical technology” (PAT) proposals as well as the traditional in-house and contract laboratories.

Today’s CGMP Reality

Though CGMP obviously requires all sample evaluation activities to meet the general requirements set forth in **ANSI/ISO 17025**, the reality is that only a few of today’s FDA-registered contract laboratories are registered to meet **ANSI/ISO 17025**, no medical product manufacturers are currently registered, or claim, to meet **ANSI/ISO 17025**, and, *except for the Agency’s forensic laboratory*, the Agency seemingly ignores this recognized consensus standard that, in conjunction with the regulations set forth in **21 CFR Parts 58, 210, 211, and 820**, clearly constitutes today’s “current good manufacturing practice” as that term is used in **21 U.S.C. 351(a)(2)(B)**.

The results of the Agency’s non-action and the industry’s failure to meet the CGMP minimum “*sample evaluation*” requirements set forth in the CGMP in a manner that meets **ANSI/ISO 17025**’s general requirements are:

1. Result values that are not sample representative and/or not valid.
2. Unexpected and “out of specification” (OOS) values whose validity is not established during the evaluation of the samples and, *in most cases*, cannot be unequivocally proven to be valid, or non-valid, in a subsequent investigation of said results – for OOS values, the investigations often state that the Analyst made a mistake or the evaluation system had a problem even though there is little or no traceable evidence supporting, much less proving, the assertions made.
3. Data that is unnecessarily uncertain and biased by the evaluators’ failing to have adequate sample evaluation procedures and controls (on the samples, evaluation environment, equipment, apparatus, and personnel) to ensure value validity.

As with CGMP compliance in general, the excuse given for not meeting the CGMP minimums for sample inspection (sampling and testing or examination) and the requirements set forth in **ANSI/ISO 17025** is that meeting them costs too much.

The truth is that such compliance failures contribute to many of the development problems that arise from the developers’ treating the results obtained **as if** they are valid certain estimates of the population from which the samples were taken **when the reality is the results obtained are often unnecessarily**

uncertain and/or non-valid estimates of the samples and/or the population from which the samples evaluated were take.

Recommended “Critical Path” Actions

1. The Agency should state that it will not accept a firm’s data and findings unless that the submitting firm can prove, and has submitted proof, that:
 - ❖ All samples and sample evaluation results meet the applicable CGMP *minimums and*
 - ❖ Samples evaluated were evaluated under conditions that met or exceeded the general requirements set forth in ANSI/ISO 17025.

[**Note:** If done, developmental and post-approval problems data related to data non-validity should become a non-issue and, *because the data values considered in any evaluation would be valid*, the conclusions reached in development from evaluating developmental data could be relied upon. Obviously, improving data reliability would facilitate development and, though the amount of initial evaluations required would increase, the overall evaluation burden should not increase and, in some cases, lessen since the repeat evaluations and additional studies that the current uncertain data environment generates will be greatly reduced or eliminated.]

2. In addition, the Agency should require each firm to certify, under penalty of law, that:
 - ❖ All the firm’s data, submitted and otherwise, was acquired in a manner that complies with the Agency’s submission expectation in **Point 1 or**
 - ❖ *For studies started prior to or within 30 days of the Agency’s issuing the data policy in Point 1*, a statement that all data and data acquisition parameters acquired have been submitted, the proof that the complete data contained therein is valid, and the firm’s plan to attain compliance within not more than twelve (12) months from the date the FDA issues this data policy.
3. For a submissions prior to the Agency’s requiring the *Point 2* certifications, a firm should be required to submit a certification that addresses the validity of the data practices used in each experiment, study, or evaluation in their submissions and, in cases, where less than *representative samples* have been evaluated, the level of confidence and uncertainty values associated with each experiment, study, or evaluation in their submissions with the understanding that if, *in a subsequent on-site inspection*, the Agency finds that the certifications provided are materially false, the Agency’s will take action under its application integrity policies against not only the firm but also those responsible officials who provided or were responsible for the false certifications.

“Critical Path” Initiative 5: Require In-Depth CGMP Compliance Assessments For All On-Manufacturing-Site and Contract-Facility Inspections

Criticality: Severe

Impact: **Universal:** All Medical Products, Developmental, New and Existing
Timeframe: **Immediate**

Introduction

Rather than adding new initiatives and taking on tasks (as this “critical path” initiative seeks to do) that are not directly the Agency’s responsibility, the Agency should focus on meeting its fundamental statutory requirement to perform **not less than** biannual CGMP compliance inspections of all the medical product industry’s product development and manufacturing facilities that are involved in the production, processing, packing, packaging, labeling, testing, quality control, or holding of any drug, drug product, biological, or device intended for or authorized for use in humans.

Instead of deploying its “limited” resources to meet its statutory inspection mandates, the Agency has chosen, under the guise of funding limitations (that actually are more conscious funds allocation than fund shortages), to abandon its statutory inspection mandate and to direct its funds into areas that do not benefit the public health – after all, the last thing that today’s knowingly non-compliant medical products industry wants is an in-depth CGMP compliance inspection (notwithstanding the Agency’s empty rhetoric about performing such inspections).

In addition, *instead of performing in-depth CGMP audits, the Agency has chosen to use a “Quality Systems” approach that, in general, not only audits paper more than actual practices but also: a) only audits, at most, a few of the seven areas the Agency has stated are sufficient to cover a CGMP inspection and b) permits skipping audits in cases where the firm’s “apparent compliance history” suggests that the firm’s prior performance indicates that a firm is **probably** in “substantial compliance” with CGMP – even though the historical record indicates that past “apparent compliance” is not a good predictor of future CGMP compliance.*

Further, *as the Agency well knows, today’s FDA continues NOT to enforce compliance with key portions of the drug and drug product CGMP regulation **minimums**, including, but not limited to:*

1. Population “representative samples,”
2. Both “scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity,”
3. Each “batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient,”
4. *For each batch, in-process “control procedures shall be established 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,”*

5. That “in-process specifications for such (in-process) characteristics” are truly “consistent with drug product final specifications,” “derived from previous acceptable process average and process variability estimates ... and determined by the application of suitable statistical procedures ...,”
6. The testing of each batch of in-process materials “for identity, strength, quality, and purity as appropriate” “during the production process, e.g., at commencement or completion of significant phases or after storage for long periods,”
7. *For each product produced*, scientifically sound acceptance “criteria for the sampling and testing” that are “adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria [that must “include appropriate acceptance levels and/or appropriate rejection levels”] “as a condition for their approval and release”) **and, to a lesser extent**,
8. The medical device CGMP regulations (*typically*, the Agency non-enforcement areas here are in those device regulations that are explicitly or implicitly the counterparts to drug product areas of non-enforcement).

Recommended “Critical Path” Actions

1. With respect to the clear CGMP *minimums* for “representative samples”:
 - a. *Minimally*, require all in the medical products industry who produces lots or batches of **discrete** units to:
 - i. Justify that the sampling and sample evaluation plans used are scientifically sound and appropriate for the samples being evaluated,
 - ii. Use the appropriate sampling and sample evaluation plans in ANSI/ASQ(C) Z1.4 for all evaluations that are sample unit examinations or sample unit classifications,
 - iii. Use the appropriate sampling and sample evaluation plans in ANSI/ASQ(C) Z1.9 for all evaluations that measure variable factor levels, **and**
 - iv. Report all of the findings from any evaluation including, the findings, the number of samples evaluated, and the statistical uncertainties and variabilities associated therewith.
 - b. *Minimally*, require all in the medical products industry who evaluate incoming, in-process and final product lots or batches of **non-discrete** units for acceptance for use or release to:
 - i. Justify that the sampling and sample evaluation plans used are scientifically sound and appropriate for the samples being evaluated,
 - ii. Prove that the samples taken are representative, sufficient in size for all of the requisite evaluations and a reserve, and not significantly biased by the sampling procedure used to sample said samples,

- iii. Prove that the sub-sample aliquots taken from the samples sampled are unbiased unit-dose (or smaller) aliquots when a variable chemical factor (e.g., active content, impurity level, excipient level) is being evaluated or, *when a critical physical factor* (e.g., particle size distribution, density, flow, intrinsic solubility) *is being evaluated*, no larger than necessary to minimize aliquot bias and satisfy the requirements for the equipment or apparatus used to evaluate said physical property,
 - iv. Evaluate a sufficient number of aliquots from each sample sampled to establish valid measures of the sample mean and sample variance for each characteristic evaluated, and
 - v. Report all of the findings from any evaluation including, the findings, the number of samples evaluated, and the statistical uncertainties and variabilities associated therewith.
- 2. With respect to the clear CGMP *minimums* for “scientifically sound and appropriate specifications, standards, sampling plans, and test procedures,” require all in the medical products industry to:
 - a. Prove that all of the *acceptance specifications* (incoming, in-process and product release) they use are statistically valid for assuring, *at the 95% confidence level or higher*, that:
 - i. Sufficient samples are tested to provide valid estimates of the population mean and variance for each factor evaluated, and
 - ii. Obtaining passing results for the samples tested predicts that the untested population will, *if tested*, meet the firm’s lifetime post-release specifications (which must meet or exceed the applicable USP or FDA-expectation *minimums* where such exist).
 - b. *Prior to release for distribution*, follow, or exceed, the requirement *minimums* set forth in any applicable consensus “standard” published by ANSI/ASQ(C), ASTM, AOAC International as well as, *post-release*, any applicable *official compendial* “standard” and any additional company-imposed or FDA-accepted post-release product performance criteria or, *where no official compendial monograph “standard” exists*, all of the company-imposed and/or FDA-accepted post-release product performance criteria.
 - c. *With respect to the clear CGMP minimums for “sampling plans,”* use “sampling plans” that “span” the population in a manner that meets the requirements set forth in **Point 1**.
 - d. With respect to the clear CGMP *minimums* for “test procedures”:
 - i. Establish that the evaluation procedures used are suitable for the purposes intended (e.g., where an “identity” test is required by CGMP, procedures that are “IDENTIFICATION” tests [like most of the USP and NF “IDENTIFICATION” procedures] should not be used since, in general, such procedures are not “identity” tests),

- ii. Use evaluation procedures that are suitable for their intended purposes.
- iii. Perform sufficient replicate measurements to ensure that the mean values determined are within 1 % relative (or less) of their true values (using the formula:

$$n = 1 + \text{Integer} (t^2 \text{RSD}^2 / d^2) \quad (1)$$

Where: **n** is the number of *measurements* that must be tested.

α is the risk level for the rejection of the firm’s hypothesis, “*batch or lot in production conforms to the firm’s specification for the variable being evaluated,*” and **(1 – α)** x 100 % is the confidence level;

t is the studentized “**t**” value at a confidence coefficient [**1-(α/2)**] for “**v**” degrees of freedom [it is okay to estimate “**v**” as the number of *measurements* taken minus one (1) in this context];

d is the allowable margin of error in %, or relatively how far from the true *result* mean are we willing to risk being; and

RSD is upper limit on the relative standard deviation in % (RSD = [SD/ \bar{x}] x 100 %) that we expect to find for the *measurements* made on the sample.

[**Notice:** **1-(α/2)**] is the correct choice for “**t**” here, as it is for all 2-sided confidence interval estimates; **1-α**] is the correct choice for “**t**” in estimating a 1-sided confidence interval.]

- iv. For each procedure, report the results found, the number of measurements made, and the procedure’s basis RSD.

3. With respect to the clear CGMP *minimums* that each “batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient,” the Agency should require those in the medical products industry who manufacture drug products to prove that the “active ingredient” level outcomes observed for *each batch* meet this requirement and not, as many firms do, the USP’s much wider, post-release, any-grab-sample-in-commerce requirements.
4. With respect to the clear CGMP *minimums* that the in-process “control procedures shall be established 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” for *each batch*, the Agency should require the covered segment of the medical product’s industry to generate and adhere to *scientifically sound* “validation” plans that extend “validation” to include each and every batch manufactured as **21 CFR 211.110(a)** clearly requires.
5. With respect to the clear CGMP *minimums* that “in-process specifications for such (in-process) characteristics” must be truly “consistent with drug product final specifications,” “derived from previous acceptable process average and process variability estimates ... and determined by the application of suitable statistical

procedures ...,” the Agency should require the medical products industry to provide proof that each of its “in-process specifications” are consistent with the drug product’s final specifications,” and “derived from previous acceptable process average and process variability estimates” and determined by the application of recognized “statistical procedures” discussed in the previous **Points**.

6. With respect to the clear CGMP *minimums* concerning the testing of each batch of in-process drug-product materials “for identity, strength, quality, and purity as appropriate” “during the production process, e.g., at commencement or completion of significant phases or after storage for long periods,” the Agency should:
 - a. *For incoming components*, require “identity” or “specific identity” tests on *representative samples* from each lot-shipment and, *for components that have a definable purity*, require tests for purity, strength, and their other critical physical and chemical characteristics on *representative samples* that define the quality of each lot-shipment of each such component, or, *for components lacking a defined purity*, require tests on *representative samples* for the critical physical and chemical characteristics that define the quality of each lot-shipment of each such component.
 - b. *For in-process materials*, require tests on *representative samples* for the critical physical and chemical characteristics that define the uniformity of the in-process materials produced during each significant phase of the manufacturing process.
 - c. *For in-process drug products being evaluated for release*, require full compliance with all of the *representative samples’* testing requirements set forth in **21 CFR 211.165**, including the currently ignored (by both the Agency and the medical products industry) clear requirements of **21 CFR 211.165(d)**, and **21 CFR 211.167**, including, for “controlled-release dosage form” products, CGMP-compliant testing (and not the sample-number deficient USP testing that the firms knowingly misuse and the FDA permits) for “the rate of release of each active ingredient” (**21 CFR 211.167(c)**).
7. With respect to the clear CGMP *minimums* for each product produced, require the medical products industry to use scientifically sound acceptance “criteria for the sampling and testing” that are “adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria [that must “include appropriate acceptance levels and/or appropriate rejection levels”] “as a condition for their approval and release”)
8. With respect to the clear CGMP *minimums* for medical devices set forth in **21 CFR 820**, require *representative samples* and comparable actions to those outlined in **Point 1** through **Point 7** for drug products in the areas of the device regulations that are explicitly or implicitly the counterparts to drug product areas.

9. Provide all Agency personnel who are involved in any aspect of the review, inspection, or acceptance activities for medical products with the in-depth training in the clear CGMP requirement *minimums* that:
 - a. Based on their statements to this commenter, the Agency's recent draft guidances, and the recent FDA Form 483s, Establishment Inspection Reports, Warning Letters and other Agency communications and positions is so obviously needed, **and**
 - b. Based on the current obvious deficiencies in the current training programs, is currently insufficient in its depth, scope and accuracy.

Summary of the “Critical Path” Initiatives

Before the Agency embarks on any new “initiatives,” the Agency should first move to enforce those sections of the clear CGMP regulations from the developmental stage onwards in a manner that fully meets, or exceeds, the clear CGMP requirement **minimums**.

The Agency’s failure to require compliance and the industry’s knowing non-compliance with the clear CGMP **minimums** have combined to create many, if not all, of the development and post- acceptance, approval, or licensing problems that the FDA, *attempting to divert attention from the Agency’s enforcement deficiencies, is, in this “critical path” initiative,* attributing to the lack of the appropriate “tools.”

Hopefully, those reviewing these comments will consider the comments made with an open mind and copies of the CGMP regulations to ensure that this commenter has dispassionately stated the comments made and, where necessary, provided supporting examples from his personal experience in the medical products industry.