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Ref: Docket No. 2003D-0380, CDER 2003136 PAT- A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, Draft Guidance for Industry Proposed Rule

Abbott Laboratories (Abbott) welcomes the opportunity to comment on the PAT draft guidance for Industry, as published in the Federal Register.

We commend the Agency on their support of innovation within our pharmaceutical industry. However, Abbott believes that continued dialogue with stakeholders is essential to convince industry to consider adopting the many recommendations of the guidance so we can partner to achieve the best results through an effective approach to serve the public health.

Abbott recognizes the FDA's continued efforts to provide draft guidances that are easy to understand and comment on. This guidance was for the most part clearly written and the inclusion of line numbers facilitated providing easily identified point of reference comments.

We also look forward to working with the Agency on revising existing guidance and/or the development of new guidance addressing such topics as strategies for calibration/recalibration of PAT technologies, treatment of unusual sample results discovered during the PAT process, etc.

While Abbott endorses the Pharmaceutical Research and Manufacturers of America's (PhRMA) response to the Agency on this proposed rule, we also appreciate your consideration of our specific attached comments. Please contact us should you have any questions.

Sincerely,

Richard Poska, R. Ph.
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Richard M. Johnson
Director, Quality Center of Excellence for Drugs

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Comments on draft guidance:
PAT- A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Docket No. 2003-0380

October 31, 2003

The following comments on the draft guidance **PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance** are provided on behalf of Abbott Laboratories.

SPECIFIC COMMENTS BY GUIDANCE LINE NUMBER

199 **Reducing cycle times by using on-, in- and/or at-line measurements**
Because cycle times can be reduced by using some off line measurements, this sentence should be reworded to something similar to "Reducing cycle times by using improved analytical techniques."

204 **Facilitating continuous processing to improve efficiency...**
Because the guidance refers to "lot" in the traditional sense of batch processing, FDA should clarify the definition of lot for the currently uncommon use of continuous processing.

389 **Process Signature.**
The concept of a "process signature" should be clarified. If documenting such a signature becomes a regulatory expectation, deviation from this signature should not be treated the same as current process deviations or OOS results. It can be difficult to correlate non-specific changes in process signature with specific changes in product quality. As a result, this approach may be extremely prone to false positives, frustrating the ruggedness of PAT methodology.

414 **Identify and measure critical material and process attributes . . .**
Although widely used, no definition exists for "critical material attribute" and "critical process attribute"- one is needed to avoid multiple interpretations.

451 **Similarly, rigorous statistical principles should be used for defining acceptance criteria for end product attributes (e.g. content**

uniformity) that take into consideration differences in the nature of the test (e.g. continuous monitoring) and sample size between an on-line test and a current laboratory test.
Requiring rigorous statistical procedures for lot release, when simple procedures will do, is an unnecessary burden on industry. Please confirm that the use of rigorous statistical principles is needed in the design of PAT methodology and that routine batch release after using PAT methods is intended to be used "statistician free".

The Agency needs to clarify if all companies producing the same product will be held to the PAT derived specification, assuming that the PAT specification is different than one derived without PAT.

Rigorous statistical tools alone may not be sufficient to define PAT end product attributes. Criteria should be defined relative to existing or proposed standards, account for increased or variable PAT sample size, and differences in reportable measures. For instance, will quality levels established by USP <905> or PDG Harmonization proposal be applicable? Shall we expect more guidance on sampling techniques as PAT sampling offer more comprehensive batch profiling options? Perhaps the recommended acceptance criteria for content uniformity should be based on a non-parametric (tolerance) approach that controls extremes, but does not set a zero tolerance limit (as found in USP <905>) because it cannot be justified.

Endorsing the use of interim specifications would help industry consider implementing PAT generated specifications for existing products.

461 **For example, batch records could include a series of charts ...**
Referencing the use of Statistical Process Control (SPC) methods would help clarify the use of rigorous statistical methods to generate meaningful charts, etc.
It would also be helpful for this section of the guidance to address the benefits of using interim specifications, which would be beneficial in implementing PAT based specifications for existing products.

521 **Transfer of laboratory analytical methods to at-line methods using test-to-test comparisons may not necessitate a PAT approach.**

Please clarify that the transfer of laboratory analytical methods only need to meet existing guidances and not a more rigorous approach as suggested by PAT.

574 **Real time release as defined in this guidance builds on parametric release for ...**
Please clarify the differences between real time release and parametric release.

642 **...that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods).**
Without specific equivalence/comparability guidance (PAT vs. current technology), PAT implementation may be inconsistently evaluated. As stated, the guidance recommends the comparison of operating characteristics of PAT vs. current USP Unit Dose Uniformity or Blend Uniformity at a quality level that has about a 50% batch acceptance probability.

For existing products, establishing tighter PAT based acceptance criteria could be problematic if PAT and existing technology are to be interchangeable or used in contingency circumstances. The guidance also lacks specific recommendations on contingency testing for PAT based technology.

727 **Bibliography**
Please consider referencing other relevant USP Guidance, specifically USP <851>, <1119>, and <1225>.