Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

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November 3, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry: Process Analytical Technology – A framework for Innovative Pharmaceutical Manufacturing and Quality Assurance [Docket No. 2003D-0380, 68 *Federal Register*, 52781, September 5, 2003]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

We appreciate the opportunity to comment on the draft guidance on process analytical technology (PAT).

The development of a guidance document on PAT is strongly supported by PhRMA. PhRMA welcomes this draft guidance and concurs with the key principles as outlined below:

- The guidance supports a scientific and risk-based approach.
- The guidance embraces both new and marketed products.
- Real Time Release based on process information is accepted as a viable alternative for the release of products.

However, PhRMA does have a number of concerns and comments. General comments are provided below. Line specific comments are attached.

1. This draft guidance provides a broad overview of the role of PAT in pharmaceutical development and manufacturing. However, it is difficult to understand many of the concepts in the guidance without a specialized background in PAT; and it is not clear how these concepts would be implemented from a regulatory perspective. Many statements are vague enough that misinterpretation is possible.

2. Harmonization of this draft guidance with other worldwide regulatory bodies is important. Without such worldwide agreement, a sponsor who develops a process with extensive PAT such that it can justify real-time release to the FDA would still need an entire quality lab dedicated to providing traditional product release testing to satisfy other worldwide agencies.

3. Risk assessment is key to the 21st Century GMP initiative including PAT. The draft guidance discusses "risk-based regulatory approaches", but doesn't mention factors such as risk to the patient, probability of an issue occurring, and the probability of the issue being detected. References or descriptions of what "risk-based regulatory approaches"

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are and procedures for performing a risk assessment or providing examples of how to perform this exercise would be very useful (e.g. risk assessment matrices presented by the FDA on multiple occasions).

4. The draft guidance is not clear on the PAT submission and review process within the agency, i.e. exactly what happens to submissions containing PAT. It would be very useful for the document to include a discussion of how a PAT submission will be handled in the agency and a flow chart demonstrating submission passage through the agency. Additionally, this flow chart should include the inspection process, further clarifying roles and responsibilities of inspectors and the Center and interactions between them.

5. To avoid misinterpretation, it would be useful for the guidance to include a glossary, which describes or defines several terms used throughout the document (e.g. critical process parameter, continuous real time quality assurance, etc.).

6. The guidance encourages introducing "PAT principles and tools" during the development phase of a product. It is conceivable that sufficient data can be generated with a PAT tool, either during the development phase or early in the manufacturing phase, leading to achieving sufficient process understanding to justify discontinuing the use of PAT. The guidance does not seem to indicate that the use of PAT could proceed through an evolutionary path, i.e. it doesn't talk about the possibility of discontinuing the use of PAT once the knowledge is acquired. Examples might include when multiple sensors are used during development, a thorough process understanding is developed and the sensors are replaced in manufacturing with an inferential or soft sensor. An alternative approach might be to continue to use the sensors used in development into manufacturing for a short period of time until the process signature shows that the process is being run the same as during development. Subsequently these sensors are removed.

7. It is unfortunate that the guidance never mentions the terms "safe harbor" or "research exemption" even though FDA has discussed those concepts several times during the past 18 months. Although a section in the draft guidance appears to refer to these concepts, it would have been better to have continued the use of the terms that had been used throughout the FDA presentations. Additionally, the safe harbor concept is one of the most contentious areas of the PAT initiative. The section describing the concept is vague and needs further clarification (e.g. how is research data defined?) The guidance should include examples of how a company can stipulate that a PAT is being used to generate research data post approval to ensure the data are not considered during a routine inspection. Furthermore, the agency appears to be reserving the right to inspect experimental PAT results by limiting the instances to "exceptional situations". This could be concerning to a company attempting to utilize PAT to improve a process. This may not encourage a company to attempt to utilize PAT, which is counter to the spirit of this initiative.

8. The increased number of tests that will be enabled through the use of PAT will provide a much more accurate view of the product's true statistical distribution. It is possible that a product, which meets all release criteria utilizing the registered release test, will fail to meet the current regulatory expectations (e.g. no product can be outside 75-125% of label claim) due to this increased data. It is suggested that the agency re-evaluate the current definition of specification limits to ensure that processes that have historically produced acceptable product are not unduly penalized by the increased amount of data enabled through the use of PAT.

9. It is not appropriate to reference documents from other regulatory authorities. We suggest that FDA remove all references to specific regional guidances (for example, the European parametric release guidance on p. 17, para.2, final sentence) in favor of a

more general statement encouraging similar concepts and approaches around the globe, including other regulatory agencies and ICH.

10. The draft guidance does not mention the word *Chemometrics*, leaving the reader to wonder if FDA endorses the use of such methods. It is suggested that this be clarified. Additionally, if a glossary is provided with the guidance, a definition of the term chemometrics could be included.

We trust that you will give careful consideration to our comments as you finalize the guidance. Please contact me if you have any questions regarding these comments.

Sincerely,

Alice E. Till, Ph.D.

CC A. Hussain

Attachment

Line Specific Comments

Page	Section	Line	Recommendation
6	III Background	109 – 127	It was noted that the bullet points were consistent with those presented in a progress report on cGMPs for the 21st Century, but they are differently worded here. It is unclear why they are included in the draft guidance and we suggest reducing or removing the paragraph and bullet points. If they are to remain, we believe that the statement concerning consistent application of "Regulations and manufacturing standards" is ambiguous versus the preceding statement on page 5 (lines 76 – 79) which refers to voluntary collaboration with the Agency to develop/ implement PAT for particular products. We suggest that this ambiguity be reconciled, such that the message is one of voluntary collaboration, on a per product basis. The bullet point could be re-phrased to read: "To ensure that the regulations and manufacturing standards are interpreted and applied consistently by both the Agency and the manufacturers".
7	III Background	130	"Throughout the life cycle of a product" - Does that mean that once an analyzer is added it has to be maintained and used as long as the product is manufactured? How does this relate to SUPAC? We suggest the sentence be clarified. See also General Comment #**Error! Reference source not found.**
7	III Background	138	Bullet one: We suggest that this sentence should read "...are ensured through the design of **robust products** with effective and efficient..."
7	III Background	142	The term "continuous real time quality assurance" has not been defined within the guidance. We suggest that it be added to the proposed glossary.
7	III Background	145-149	This section discusses "risk-based regulatory approaches", but doesn't mention factors such as probability of an issue occurring and the probability of the issue being detected. References or descriptions of what "risk-based regulatory approaches" are would be very useful. See also General Comment #**Error! Reference source not found.**
7	III Background	158 – 161	This paragraph defines the framework for PAT; however we find it extremely ambiguous and request it be rewritten in order to clarify the message. We suggest the following wording: "For the purpose of this draft guidance, PAT is defined to be a system of activities aimed at designing, monitoring, analyzing and controlling manufacturing in order to ensure final product quality. This

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			may be accomplished through the timely identification and measurement of critical to performance attributes of the raw materials, in-process materials and the processes themselves. The overall objective is to enhance process understanding, which may ultimately lead to process control utilizing timely measurements (i.e. during processing)."
8	IV PAT Framework	168-179	The bullet points are important considerations for setting product specifications but don't seem to have anything to do with building quality into a pharmaceutical product. Quality is built into a product through process understanding to achieve a product's specifications that should be set by the customer's wants and needs. Thus we suggest that this paragraph and associated bullet points be rephrased. If the bullet points are to be maintained, we suggest that bullet 3 should be separated into two bullets, as follows: - • The selection of excipients based on their functionality and the drug attributes listed above; • The selection of packaging components and design based on product and patient need.
8	IV PAT Framework	199-207	The following gains were not listed yet featured prominently later in the document o Use of in-process control and feedback o Process understanding We suggest that the above be added to the list.
8	IV PAT Framework	201	The statement "preventing rejects, scrap, and re-processing" infers that these issues will not occur which is not accurate. We suggest a better choice of words might be "minimizing the occurrence of rejects, scrap, and re-processing".
9	A: Principles and Tools	233-246	We suggest that this paragraph is a rather simplistic way of considering modern formulation development. Many formulation strategies are generalized and technologies exist (e.g. expert systems) to guide robust product and process development. In addition, many attributes are tested without separation of the active ingredient. Thus, this paragraph should be modified. We suggest removing the second sentence ("Because these strategies...") and expanding the third sentence to read: "Currently, in-process materials and end products are tested in general off-line after preparing collected samples for analysis."
12	A: Principles and Tools: PAT Tools	349-355	It is not clear how PAT is connected to the first bullet point. We suggest that it be modified to read: "What are the implications of process changes upon the degradation or dissolution properties of the drug substance or product?"
12	Process Analyzers or Process Analytical Chemistry Tools	369-379	We suggest placing the types of measurements, i.e. off-line, on-line, etc. into the PAT Framework section, e.g. in general description text connected to lines 158-163.
14	Process	437-	An additional description of what acceptable process times

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	Monitoring, Control, and End Points	441	(process window) are would be very useful (include a definition or description in suggested glossary). As written, it would be very easy for this to be interpreted to represent the current endpoint as defined prior to PAT.
14	Process Monitoring, Control, and End Points	445-455	We seek clarification of the intention of the Agency with regard to this paragraph. Our interpretation of the paragraph seems to contradict the risk-based approach, which forms the basis of the guidance. We believe that **statistical process control** (SPC) needs to take into account the level of process understanding and process capability and increased sampling may not be appropriate where it would not add value to the quality decision. See also General Comment #**Error! Reference source not found.**
14	Process Monitoring, Control, and Endpoints	458-459	It would be useful to include examples of what is meant by "Certain data are likely to be relevant for routine quality assurance and regulatory decisions."
14	Process Monitoring, Control, and Endpoints	459	Further clarification is sought to specify the boundary between uses of PAT as a regulatory-filed test versus an in-house process control tool. See also General Comment # **Error! Reference source not found.**
14	Process Monitoring, Control, and Endpoints	461	In the context of this paragraph it would be useful to reference the use of SPC methods to establish batch limits. Additionally, the draft guidance does not address the concept of interim specifications, which are very useful when implementing PAT. Inclusion of a discussion on this subject would be very beneficial.
14	Process Monitoring, Control, and Endpoints	463	Why would batch records include both "inter- and intrabatch" records? We suggest removing the words *inter- and intrabatch* from the text.
14	Process Monitoring, Control, and Endpoints	469 - 470	"and provide alternative, effective mechanisms to achieve validation." The statement suggests that we can dispense with the 3-batch validation approach and move to a continuous quality verification system using PAT as an alternative to the 3-batch approach. If this is the message, we suggest clarifying and increasing the emphasis by adding the following sentence at the end of the paragraph: "Thus the conventional three batch process validation approach becomes one of the alternatives for process validation."
15-16	Process Understanding	508-525	The text is confusing. We suggest shortening this section and clarifying concepts the author is trying to cover.
18	Regulatory Strategies	622-624	It is unclear what is meant by "mechanistic-based regulatory specifications". Does this refer to specifications for raw materials or final product? It seems applicable to raw

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			materials, but it's not clear why it applies to drug product unless it is referring to the mechanisms that are important for the drug's delivery or action.
18	Regulatory Strategies	631-633	It is unclear whether data that is for information only or research data needs to be kept? We note that at this stage of method development, data will probably not be a part of batch records.
18	Regulatory Strategies	626-646	It's not clear how FDA intends to inspect processes that use PAT "based on current regulatory standards (e.g. test results from currently approved or acceptable regulatory methods)." What constitutes an "acceptable regulatory method"? This appears to contradict the effort by FDA to encourage use of PAT, since current regulatory standards may not necessarily be meaningful for every PAT application. Does this imply that routine FDA inspections are different from PAT FDA inspections? We suggest inserting clarifying language. The term 'Research Data' requires additional clarity to distinguish between research data generated during product and process development in R&D and research data generated as a PAT sensor trial or to explore new technologies. Lastly, the strategy presented here seems to be in conflict with a strategy on the same subject presented by the Agency on several occasions. The latter suggests that if an atypical PAT result is encountered but the product meets regular release specifications, the product may be released while the atypical PAT event is being investigated. See also General Comment #**Error! Reference source not found.**
18	Regulatory Strategies	638	The use of "...trends affect quality" doesn't make sense. Trends are derived from the collected data. They don't, in themselves, "affect quality" but may be used to draw conclusions about the product's quality. We suggest rephrasing the sentence to "trends indicate an effect on quality".
20	V. PAT Regulatory Approach	702 - 703	We suggest that it is unclear which of the implementation options listed is applicable in which circumstance. We request clarification in this regard. See also General Comment # **Error! Reference source not found.**
20	V. PAT Regulatory Approach	718-721	The Agency should consider the use of comparability protocols of which its contents are designed to apply to multiple products or processes at one time.
21	Useful Standards	727-752	The listed ASTM standards are not all currently applicable to pharmaceutical use as written. We suggest that if ASTM standards are to be referenced, then a new standard should

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		402-407	be produced that is meaningful for the pharmaceutical industry. It is agreed that incorporating relevant content from particular ASTM standards can have value for application to PAT systems and data analysis. We suggest adding the following statement in this section: "Concepts and principles in the listed ASTM standards may be useful for reference and defining certain concepts related to PAT systems and data analysis." Final scientific rationale as to which standard is used is dependent on the application scenario and rests with the originator of the method.