Groton Laboratories
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Global Research & Development

October 30, 2003

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

Re: Docket No. 03D-0380, Draft Guidance for Industry: Process Analytical Technology (PAT)- A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance.

Pfizer would like to acknowledge the effort put forth by the FDA in the publication of the Draft Guidance for Industry on PAT- A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. It is recognized that great effort has been made to encourage Industry to develop and implement PAT. Pfizer appreciates the opportunity to provide the attached comments to further clarify and strengthen the proposed guideline.

Sincerely,

Sonja Sekulic, Ph.D.
Assistant Director ARD
Groton Laboratories
Pfizer Inc.

Randall Schadt, Ph.D.
Manager/Team Leader
Global Manufacturing Services
Pfizer Inc.

October 30, 2003

Pfizer Inc.

Comments concerning Draft FDA Guidance: "PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance - August 2003"

We are supportive of this draft guidance document's intent to provide a regulatory framework to encourage pharmaceutical manufacturers to develop and implement "Process Analytical Technologies" (PAT).

We believe that the draft would benefit from some modification to its current structure and content.

We offer below our comments on strategic issues, together with specific recommendations concerning modifications to guidance content, which we believe will enhance the document's clarity and succinctness.

1. Strategic Issues:

Remit of Regulatory Guidance

We recommend that this guideline be aligned with the ICH topics on P2, Quality Systems and Risk analysis, and other equivalent global regulatory initiatives.

Content and Order

We note that, once finalized, the guidance is intended to represent the Agency's current thinking on PAT. We suggest that, to aid understanding, the draft guidance would benefit from a reduction in its current content, so that it focuses upon the high – level regulatory and manufacturing aspects of PAT. We believe that such refinement would facilitate industry's understanding of Agency thinking with respect to PAT, hence smooth industry uptake of PAT concepts and approaches.

The table below contains our specific recommendations concerning modifications to guidance content, and specifies those elements of content that we believe should be removed.

2. Specific Comments - Content Recommendations

Page	Section	Line	Recommendation
5	II Guidance development	54 - 65	Recommend that content describing the supportive historical/ political context to the PAT initiative should be removed from the guidance.

Page	Section	Line	Recommendation
	process and scope		
5	II Guidance development process and scope	70 - 72	Suggest there should be more inclusive text pertaining to drug substance because the guideline says it is applicable to drug substance and intermediates, yet from that point onwards it is essentially silent on drug substance and entirely focused on drug product philosophy. Example: Line 248 change to (e.g., blend for 10 minutes, or allow to react for 20 minutes)
6	III Background	90 – 100 and 102 - 127	Recommend that content describing the supportive historical/ political context to the PAT initiative should be removed from the guidance.
6	III Background	122 - 123	Suggest 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 should be reconciled, such that the message is one of voluntary collaboration, on a per product basis.
7	III Background	130	In reference to "Throughout the life cycle of a product", we suggest inclusion of the following sentence. "During the lifecycle of a product, it may be necessary to modify or retire techniques or technologies with appropriate scientific rationale".
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	"continuous real time quality assurance" - the term has not been defined within the guidance. We propose that the following definition is included. 'Operations that monitor, control, and/or analyze critical quality attributes through use of PAT and manufacturing execution systems such that quality of processes and products are appropriately verified while manufacturing is in progress.'
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. Suggestion: For the purpose of this draft guidance, PAT is considered to be a system of activities aimed at designing, monitoring, analysing and controlling manufacturing in

Page	Section	Line	Recommendation
			order to ensure final product quality. This 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).
7	IV PAT Framework	165	Suggest change of text to read... The goal of PAT is to understand the process. This will allow for control of the manufacturing process via utilization of appropriate manufacturing execution systems. This initiative is consistent with our current.....
8	IV PAT Framework	175	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.
9	A: Principles and Tools	233 - 246	This paragraph constitutes a rather simplistic way of considering modern formulation development. Many formulation strategies are generalised 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. Suggest that it be abbreviated to focus on the additional information that is obtained via the use of PAT techniques and the non-destructive nature of these types of analyses.
10	A: Principles and Tools	290	The word chemometrics has not been used in this guidance. We propose inclusion of chemometrics as a tool and offer the following definition as an example. The chemical discipline that uses mathematical, statistical and other methods employing formal logic to • design or select optimal measurement procedures and experiments • provide maximum relevant chemical information by analyzing chemical data
11	A: Principles and Tools: PAT Tools	317 - 337	The information contained within these two paragraphs is not relevant to the guidance document; and suggest that these paragraphs should be deleted.
12	A: Principles and Tools: PAT Tools	349	(Bullet 1) Suggest that mechanisms of degradation and absorption are outside the remit of PAT. We propose that bullet 1 read:

Page	Section	Line	Recommendation
			What are the implications of process changes upon the dissolution properties of the drug substance or product?
12	Process Analyzers or Process Analytical Chemistry Tools	371	(Bullet 3) Suggest that the following change: "on-line where measurement system ...." to " on-line where the measurement system ...."
12	Process Analyzers or Process Analytical Chemistry Tools	369-379	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.
12	A: Principles and Tools: PAT Tools	379 - 386	Suggest that it is not always necessary to correlate multivariate analyses to a primary method of analysis; instead, multivariate analyses may be considered in isolation, and the guidance should be modified to reflect this. Examples of circumstances when its not always necessary include blend uniformity, API endpoint determination, drying process monitoring could all be accomplished without direct correlation to a reference technique or complex mathematical treatments.
14	Process Monitoring, Control, and Endpoints	463	With reference to "inter- and intrabatch ", we propose that systems for trending and tracking inter-batch data do not require storage of such data with every individual batch record. Suggest deletion of "(inter- and intrabatch)".
14	Process Monitoring, Control, and Endpoints	469 - 470	" and provide alternative, effective mechanisms to achieve validation." Suggest adding sentence: This confirms that in a PAT environment, the 3 batch validation process becomes just one of several alternatives to achieving process validation.
15-16	Process Understanding	508-525	Text is confusing. Suggest shortening this section and clarifying concepts the author is trying to cover.
16	Process Understanding	526-530	For improved understanding, we suggest that the beginning of paragraph is rewritten as: Structured product and process development on a small scale, using experimental design and an on- or in-line process analyzers to collect data in real time will provide valuable insight and understanding for process optimization, scale-up, and technology transfer (e.g. kinetics of reactions, reaction end-points, crystallization, powder blending etc.). Process understanding.....

Page	Section	Line	Recommendation
16	Process Understanding	557 549 - 557	Suggest removal of the statement referring to the company's internal management support. In place of "Integrated Systems Approach" the title and subject matter should refer to manufacturing execution systems.
17	Regulatory Strategies	579	Remove reference to specific regional guidance's (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.
18	Regulatory Strategies	618 – 621 626 – 633	Suggest that some useful introductory information is located towards the end of the draft guidance, and that it would be helpful if this were to form part of a revised introduction
18	Regulatory Strategies	631-633	Do we need to keep data that is for information only or research data? Note that at this stage of method development, data will probably not be a part of our batch records.
18	Regulatory Strategies	635-646	We recommend that routine FDA inspections should be different from PAT FDA inspections, therefore the phrase 'acceptable regulatory methods' should be deleted since current regulatory standards may not necessarily be meaningful for every PAT application.
19	Regulatory Strategies	662 - 666	Suggest that some useful introductory information is located towards the end of the draft guidance, and that it would be helpful if this were to form part of a revised introduction
		670	Suggest removal of the word "new" from' new FDA PAT team'.
20	V. PAT Regulatory Approach	702	Suggest that it is unclear which of the implementation options listed is applicable in which circumstance. For example, we suggest that flow charts are included to present the review processes for plans submitted for PAT and post –submission of applications.
20	V. PAT Regulatory Approach	716-719	Use of a comparability protocol could be beneficial particularly if its contents are designed to apply to multiple products or processes at one time
20	V. PAT Regulatory Approach	724	Type: should read " Manufacturers"
21	Useful Standards	727-752 402-	The listed ASTM standards are not all currently applicable to pharmaceutical use as written. Suggest that if ASTM standards are to be referenced, then a new standard should be produced that is meaningful for the pharmaceutical

Page	Section	Line	Recommendation
		407	industry. It is agreed that incorporating relevant content from particular ASTM standards can have value for application to PAT systems and data analysis. Suggest statement in this section should be added to state '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.