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August 27, 1999

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

Re: [Docket No. 99N-0193] Proposed Rule; 21 CFR Parts 5, 206, 250, 314, 600, and 601; Supplements and Other Changes to an Approved Application

Dear Madam or Sir:

PDA is pleased to have the opportunity to provide comments on the proposed rule, *Supplements and Other Changes to an Approved Application*, which was published in the *Federal Register* on June 28, 1999. We trust PDA's comments will assist FDA in issuing a science-based final rule that will clearly define the requirements for changes requiring supplement submission and prior approval, changes requiring supplement submission 30 days prior to distribution, changes requiring supplement submission at time of distribution, and changes to be described in an annual report.

PDA strives to assess regulatory issues primarily on their scientific and technical merits. To facilitate FDA review, our comments are divided into two parts: this cover letter which describes our general concerns, and a table which explains specific comments by section.

General Concerns

- Overall, there is little or no reduction in reporting requirements. The regulation suggests that by using the combination of guidance and regulation, flexibility is gained and there is increased potential for reducing reporting requirements as knowledge is gained. Such reductions in reporting requirements are not evident in the proposed rule, and in fact, we believe there will be an increase in the number of submissions. In particular, we are concerned about the number of changes classified as preapproval supplements. This burdensome categorization is often not warranted and we recommend more frequent use of the CBE-30 supplement.

- We recognize that FDA is using the word "validate" (assess the effect of a manufacturing change) in the same sense as Congress's use of this word in FDAMA. We understand that within the guidance, it is not intended to have the same meaning as the CGMP definition of

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"validate." However, use of the same word for different meanings could result in unnecessary confusion and could create the potential for regulatory "drift." PDA recommends replacing "validate" with "assess" in the proposed rule.

- Changes that significantly affect sterilization are considered major changes requiring prior approval supplements. However, we encourage FDA to re-evaluate the examples used in the companion guidance document and reconsider if many of these can be lower reporting categories. In addition, many of the examples provided in the guidance for sterile process changes should not require regulatory reporting but should be documented internally by the applicant and available for field CGMP inspections.

- PDA is pleased that the proposed rule retained the provision which allows applicants to make a change in accordance with a regulation or a guidance that provides for a less burdensome notification of the change (such as SUPACs). PDA recommends that the time frame between the final rule and the revision of the SUPAC documents be kept short to minimize confusion. During the transition period, the industry would use whichever document provides the least burdensome regulatory requirement (i.e., lowest reporting category).

- We understand that after November 20, 1999, and until the final regulation for section 314.70 publishes, section 506A will be the sole basis for FDA's regulation of postapproval manufacturing changes. PDA recommends that FDA publishes the final rule as soon as possible to minimize confusion during the transition period when section 506A will govern changes.

- PDA feels that there is no need to distinguish "natural protein product, a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonol antibody" from other products. These products should be regulated no differently than other, traditional products.

- PDA recommends that the proposed rule be reworded to clearly state that a comparability protocol if not submitted in the original market application can be submitted as a supplement, post approval. The additional clarification is consistent with the intent and actual practice.

- PDA recommends that general statements such as "may," "any changes," "but not limited to," should be avoided. These "catch-all" phrases can be easily misinterpreted by field inspectors. In fact, the industry is experiencing this today with 314.70(g) and 601.12. Instead, FDA should be more specific. In our comments, we have suggested adding the modifier

"significant" or "significantly" in several instances to sharpen the intended meaning. Since the term "significant" is itself undefined, PDA suggests that in the context we use it in our comments "significant" means "likely to adversely affect the identity, strength, quality, purity or potency of the related product."

We appreciate the opportunity to contribute to the development of this proposed rule. Please contact me if you have any questions.

Sincerely,

Edmund M. Fry
PDA President

Attachment

Section	**Comment**	**Rationale**
Section 314.3 **Definitions**	While we recognize that section 506A(c)(1) of the act contains these terms, we recommend replacing the terms *validate* or *validation* with *assess* or *assessment* throughout the proposed rule and draft guidance document.	The term *validate* or *validation* defined in this section means assessing the change, and is not intended to mean the same as the CGMP definition of validation. We feel the inconsistent use of the same terms for different meanings lends itself to unnecessary confusion.
Section 314.70(a)(3) **Supplements and Other Changes to an Approved Application**	This section allows applicants to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change. We are pleased that this provision of current 314.70 is present in the proposed rule. It is instrumental in permitting less burdensome reporting mechanisms for changes (such as SUPAC guidances).	
Section 314.70(a)(4)	We recommend revising this section from "*...in accordance with this section*" to "*...in accordance with paragraphs (b) and (c) of this section.*"	Many labeling changes are minor and prompt revision of associated promotional labeling and/or advertising is not warranted (such as proposed 314.70(d)(2)(x)&(xi)).
Section 314.70(b)(2)(i) **Changes requiring a Prior Approval**	We recommend that changes to comply with an official compendium (such as USP-NF standards) should be an annual reporting category.	This requirement is more stringent than the current 314.70 and will substantially increase regulatory burden and add time (delays) in industry's ability to make product improvements.
Section 314.70(b)(2)(iii)	We recommend changing the section to read "Changes that significantly impact the sterility assurance, ..."	The statement "may affect product sterility assurance" is vague, broad and restrictive and could be interpreted conservatively, resulting in increased regulatory burden. We also encourage FDA to re-evaluate the examples in the companion guidance document and reconsider if many of these can be lower reporting categories.
Section 314.70(b)(2)(v)	Clarify "Changes in labeling ..." to "Changes in drug product labeling..."	API labeling changes need not be submitted to the registration.

Section	**Comment**	**Rationale**
Section 314.70(b)(3)(vi)	We recommend that this section be deleted; we do not feel there is a need for different requirements for these products.	This information (relevant validation protocols) is available for review on-site. Should the FDA disagree and feel that special requirements are warranted, we recommend these specific details be more appropriately captured in the Guidance instead.
Section 314.70(b)(3)(viii)	We recommend that this section be deleted.	Currently CGMP validation information, including a reference to appropriate SOPs, is required only as it pertains to sterilization processes and biologic products [601.12 (3)(vii)]. The proposed paragraph implies that a reference to appropriate SOPs is required for all changes. We feel it is not necessary to include reference to appropriate SOPs in the submission for any type of change including sterilization process changes, or changes to biologic products.
Section 314.70(c)(2)(i) **Changes Being Effected Supplement**	We recommend the revising this section from "*...a change in the container closure system that does not affect the quality...*" to "*...a significant change in the container closure system that does not adversely affect the quality...*"	Additional clarification; the original wording could be interpreted broadly.
Section 314.70(c)(2)(ii)	We recommend that this section be deleted.	These products should not be regulated differently than the traditional products. Should FDA disagree and feel that this requirement is warranted, we recommend the specific details be captured in the Guidance instead.
Section 314.70(c)(6)(i)	We recommend that changes to comply with an official compendium (such as USP-NF standards) should be an annual reporting category.	This requirement is more stringent than the current 314.70 and will substantially increase regulatory burden and add time (delays) in industry's ability to make product improvements.

Section	**Comment**	**Rationale**
Section 314.70(d)(2)(i) **Changes for Description in an Annual Report**	We recommend this statement be revised to "*Any change made to comply with an official compendium.*" Delete the remaining sentence.	Our recommendation is consistent with current 314.70(d)(1). The additional wording in the proposed rule would increase regulatory burden; and is unwarranted.
Section 314.70(d)(2)(iii)	We recommend that "Replacement of equipment with that of the same design and/or different operating principles" should be described in the annual report for all drug products.	Natural protein products, etc., should not be regulated differently than other products.
Section 314.70(d)(2)(vi)	We recommend deleting the phrase "full production batches."	Current 314.70(d)(5) allows "extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application." There is no requirement today for the data to be on full production batches. This requirement would unnecessarily increase regulatory burden and is unnecessarily restrictive.
Section 314.70 (d)(3)(i)	Consistent with Comment 1, we recommend revising "*...the effects of the change have been validated*" to "*...the effects of the change have been assessed.*"	The term *validate* or *validation* defined in this section means assessing the change, and is not intended to mean the same as the CGMP definition of validation. We feel the inconsistent use of the same terms for different meanings lends itself to unnecessary confusion.
Section 314.70(e) **Protocols**	We recommend a revision from "*...shall be submitted as a supplement*" to "*if not approved as part of the original application, shall be submitted as a supplement...*"	The revised wording provides additional clarification that is consistent with current practice.

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