ANIMAL
HEALTH
INSTITUTE

Representing manufacturers of animal health products

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President & CEO

December 1.5, 1999

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

Re: Docket No. 99N-1415 – Proposed Rule "Supplements and Other Changes to Approved New Animal Drug Applications"
Docket No. 99D-1651 – Draft Guidance "Guidance for Industry - Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA"

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments in response to the referenced Proposed rule published by the Food and Drug Administration in the *Federal Register* on Friday, October 1, 1999, (and the referenced Draft Guidance document) to amend its regulations on supplements and other changes to an approved new animal drug application (NADA) or abbreviated new animal drug application (ANADA) to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modem food production, and the medicines that keep livestock and pets healthy.

Because the documents are nearly identical, AHI fully endorses the comments made by the Pharmaceutical Research and Manufacturers of America in their letter and Table of Specific Comments submitted on August 27, 1999 to Docket No. 99N-0193 "Supplements and Other Changes to an Approved Application" and Docket No. 99N-0193 "Draft Guidance of Industry on Changes to an Approved NDA or ANDA" (copies attached). In addition, a list of specific issues critical to the animal health industry are highlighted in Attachments I and II for your consideration.

In general, AH1 member companies are concerned and disappointed that FDA's proposals published on October 1, 1999 do not meet either the intent of Congress or Section 116 of the FDA Modernization Act. The intent of Congress as captured in Senate Report No. 105-43 was that Congress expected FDA to achieve substantial improvement in the management of technical supplements for manufacturing changes. A few key quotes from that report follow:

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"In the past, the FDA has imposed very stringent limitations on the ability of pharmaceutical and biotechnology industries to adopt new manufacturing procedures."

"The impact of past FDA policy in this area on the pharmaceutical and biotechnology industries has been substantial."

"To address these problems, the legislation considered by the committee included a new approach to manufacturing changes for new drugs and biological products."

A careful analysis of the October, 1999 proposed rule shows that, not only is there not significant regulatory relief embodied in these proposals, these proposals in fact add significant numbers of additional new categories of manufacturing changes for which FDA would require prior approval supplements. Nor are there new approaches to regulations for manufacturing changes embodied in the proposed new rule and guidance.

Given the intent of the FDA Modernization Act, one would have expected the accompanying draft guidance to include new opportunities for reduced reporting requirements. However this is not the case. Some of the key areas in the guidance include changes such as:

- **Sterile processes -** 11 categories for prior approval supplements are described in the guidance;

- **Natural (protein) products** – special emphasis has been added for natural products and significant new restrictions are placed on manufacturing changes. In addition, three new categories of prior approval supplements are listed in the draft guidance for such products;

- **Packaging** – packaging changes are the most scientifically straightforward of manufacturing changes for a company to evaluate and are the least risky in terms of potential implications, yet four categories of prior approval supplements are specified here as well;

- **Specifications -** the proposed guidance includes an expansion of the International Conference on Harmonization (ICH) definition of specifications that would include raw material controls, in process tests, packaging component controls, etc.;

- **Reporting of items not previously reported at all -** the draft guidance includes reporting requirements for changes to reference standards, secondary packaging components and environmental controls, etc.; and

- **Reporting requirements for items that are covered more appropriately by Current Good Manufacturing Practices (cGMPs) (21CFR Part 210 and 211) -** the draft guidance includes requirements for reporting Standard Operating Procedures (SOPs) and Validation Protocols for all products, items previously not required.

While it could be argued that some of the prior approval categories are not "new" because such changes would have required prior approval supplements under the current regulation, under the FDA Modernization Act they all should have been appropriately reconsidered as CBEs or annual reportable items.

Counterbalancing these multiple additions of prior approval supplements are just a few additions to the list of annual reportable changes (e.g., interchanging of metal and plastic screw caps; changes in or addition of a bottle seal; changes to antioxidant, stabilizer or mold releasing agents in the resin of bottles for solid oral dosage forms; and a move to a new labeling site) and a provision for handling multiple changes which will provide needed clarity to address a common concern with SUPAC-IR for example.

On balance the reporting burden under the proposed rule and draft guidance would not be reduced but rather would be substantially increased.

Furthermore, FDA has generated the additional categories of prior approval supplements listed above without providing any evidence of the need or a scientific rationale for such additional requirements. FDA has not presented evidence of the substantial adverse impact of any of the whole series of new categories of prior approval supplements which it has proposed in the proposed rule and the accompanying draft guidance. The requirement for FDA to present such evidence was a clearly stated expectation during the development and enactment of the manufacturing changes provisions of the FDA Modernization Act.

In addition, the proposed increase in the reporting burden comes despite the specific provision in the FDA Modernization Act for the manufacturer (application sponsor) to have assessment data regarding the proposed change at the time of the submission of manufacturing change supplements. The FDA Modernization Act specifies that a drug made with a manufacturing change may be distributed only after completing studies that assess the effects of the change (defined as "validation," sec 506a (1)). The legislative intent of the FDA Modernization Act is that if appropriate studies comparing pre- and post-change material are performed and no evidence of an adverse effect is found, then a reduced reporting structure for the evaluated changes is appropriate. The logic for this is inescapable: a given proposed manufacturing change can indeed have substantial potential for adverse effects at its inception, when little might be known about the impacts of the change. However, once actual material has been made with the change and assessment studies have been successfully completed most or all of the potential impacts of the change have been eliminated. Thus the assessment information showing no adverse effect from the proposed change should permit a reduced reporting requirement under the FDA Modernization Act. This is a critical element of the statutory change enacted by the Congress and signed by the President.

Additionally, it must be noted that the animal drug industry has been very pleased with the successful 1996 CVM initiative, "Alternate Administrative Process for the Implementation and Submission of Supplemental Chemistry, Manufacturing and Control Changes (AAP)." In

fact, the AH1 support of FDAMA was given based on our legal interpretation that FDAMA did not preclude the continuation of the AAP program.

The AAP program very succinctly provides a process for determining minor supplemental chemistry, manufacturing and control changes that are reported on a biennial basis. AHI continues to strongly support the concepts embodied in the AAP and is concerned that implementation of the proposed rule will be more burdensome, on both FDA and industry, than the AAP. CVM and AH1 member companies have had three years of successful implementation of this program and believe that the proposed rule will be a significant step backwards.

Thank you for the opportunity to provide comment and express our concern regarding this proposed rule and guidance document.

Sincerely,

Alexander S. Mathews

Attachments

Attachment I
514.8 Proposed Rule Comments

The comments below are referenced by the page number of the Federal Register notice of October 1, 1999 and by a specific paragraph reference in the proposed rule.

1. [Page 53291, middle column] 514.8 (a) (ii) – Clarify the requirement for the submission of the minor changes and stability report "within 60 days of the anniversary date of the application's original approval or a mutually agreed upon date" to note that this time frame extends before and after this agreed upon date.

2. [Page 53291, middle column] 514.8 (a) (iv) – The word validate should be removed from this rule. Validation has a specific meaning within the industry and refers to cGMP validation. The word "assess" is more appropriate for the context of this document. This comment applies to everywhere the word validate or validation occurs. Changing to "assess" will avoid confusion within the industry.

3. [Page 53291, last column] 514.8 (b)(1)(ii) – Change "validate" to "assess." (See note above).

4. [Page 5329 1, last column] 5 14.8 (b)(l)(iv) – Delete the requirement for a copy of each supplemental application to be sent to the appropriate district office. Many district offices have neither the space to store these documents nor the need for all submission documents. Any submission documents desired or required by the district office are available either from the Document Center, by request from the manufacturing site or at the manufacturing site during an inspection. Requiring copies to be sent to the district offices is a non-productive use of both industry and agency resources. This requirement is opposed to the goal stated for this rule and the intent of FDAMA.

5. [Page 53292, first column] 5 14.8 (b)(2)(iii)(H) – Delete the requirement for the submission of validation protocols for "natural products, et. al." Validation protocols are maintained at the manufacturing site and are more appropriately reviewed on site. Requiring submission of validation protocols for natural products only is a new and additional requirement without any greater assurance of safety or efficacy of these products. This additional regulatory burden is in opposition to the goals of the proposed rule and to the intent of FDAMA. There is no scientific rationale for singling out natural products under this requirement. In addition, there is no clear definition of these products. The accompanying guideline states that natural products include products derived from microorganisms. Many products, including antibiotics, are derived from microorganisms and have been produced and used for many years, some for decades, with adequate controls on manufacturing changes and no adverse effects. Requiring submission of validation protocols for only this single class of products is excessive.

6. [Page 53292, middle column] 5 14.8 (b)(2)(v) – Delete or modify the requirement that protocols "must be submitted as a supplement requiring approval for FDA prior to distribution of the product." This requirement will have an effect opposite of the intent of

FDAMA. Submission as a supplement subjects protocols to a 180-day review timeframe. Currently, such protocols are reviewed in a 30 - 45 day timeframe. Extending the review timeframe will delay implementation of changes contrary to the stated purpose of this rule. The statement noted above should either be deleted or a 30 day review timeframe specified.

7. [Page 53292, middle column] 514.8 (b)(3)(ii)(B) – The higher classification of changes for natural products as moderate changes is inappropriate. The types of changes listed in this section should be evaluated on the potential for adverse impact on safety or efficacy of the product. The examples given including (1) an increase in production scale during finishing steps involving new or different equipment and (2) replacement of equipment with that of similar, but not identical design that does not affect the process methodology or process operating parameters should be classified as minor changes to be submitted in the annual report. As with other products, changes in scale and replacement of equipment for natural products that do not change operating parameters have a minimal chance to impact product safety or efficacy. There is no scientific basis for singling out all natural products under this requirement. In addition, there is no clear definition of these products. The accompanying guideline states that natural products include products derived from microorganisms. Many products, including antibiotics, are derived from microorganisms and have been produced and used for many years, some for decades, with adequate controls on manufacturing changes and no adverse effects. The additional regulatory burden contained in this section is in opposition to the goals of the proposed rule and the intent of FDAMA. This section should removed and natural products included with all other products under section 514.8 (b)(4).

8. [Page 53293, first column] 514.8 (b)(4)(ii)(C) – Delete the words "except for equipment used with a natural product, a recombinant DNA-derived protein/polypeptide product." As noted above, singling out these products by requiring a higher classification of these changes is inappropriate. There is no scientific basis for a blanket application of this distinction. All changes should be assessed on their potential for adverse affects on the safety or efficacy of the product. Changing equipment for natural products (as defined in this rule) should be evaluated on the same basis as all other products. The comments stated for paragraphs 514.8(b)(3)(ii)(B) regarding the broad application of this definition and the history of the safety of these products applies here.

9. [Page 53293, middle column] 5 14.8 (b)(4)(iii)(C) – This section should be modified to state "Either the date each change was made or the first lot produced using the change." For processes that take several days, the first lot number is more appropriate than the date. The lot number allows traceability through the entire process to better determine the effect of the change.

10. [Page 53293, middle column] 5 14.8 (b)(4)(iii)(F) – Requiring the submission of batch records with changes highlighted is an unnecessary additional regulatory burden that will not increase the assurance of the safety or efficacy of products. Batch records may be issued or reissued to correct minor typographical errors or to clarify instruction. Several versions may be issued in one year. Requiring the highlighting of all of these changes in the annual update is unnecessary. Batch records and their history are maintained at the manufacturing site and

are available for review during inspections. The requirement to submit highlighted batch records will impose a significant additional burden upon the industry with no corresponding increase in safety, purity, or efficacy of products. This requirement is in opposition to the goals of this proposed rule and the intent of FDAMA.

11. [Page 53293, last column] 5 14.8 (c)(2)(C)(3) – Remove the reference to 514.80. This refers to a non-existent rule. 5 14.80 was proposed on December 17, 199 1. However, this rule has never been issued as final. While FDA has stated its intention to finalize this rule, currently, 514.80 does not exist. This reference appears to be an attempt to issue a rule in final form without following standard FDA procedure. As the proposed rule has been dormant for eight (8) years, there can be no expectation that 514.80 will be issued as originally proposed. A revised version does not yet exist. Therefore, the reference to this obsolete proposal should be deleted.

12. [Page 53293, middle column and last column] 514.8 (c) – This section appears to eliminate the ability to report minor changes to labeling in an annual update. Label changes are classified as major changes (5 14.8 (c) (2)) or requiring a written notice of a supplemental application - Changes Being Effected (5 14.8 (c)(3)). AH1 requests that this section be clarified and the opportunity to submit minor changes in an annual update be added. Labeling changes unrelated to product efficacy or safety should be permitted as minor changes and included in annual reporting. The accompanying guidance document should be expanded to address labeling changes.

Attachment II
Comments on Guidance for Industry
Chemistry, Manufacturing and Control
Changes to an Approved NADA or ANADA

These comments address specific concerns with the guidance document issued to accompany the proposed revisions to 2 1 CFR5 14.8

1. Line 92 - This sentence should be deleted. Providing a copy of all supplemental applications to the district office is unnecessary. Some district offices have no space to store these documents, nor, do they bring them to the facility when conducting inspections. Copies of submissions are available for district personnel at the plant site, from the FDA Document Center or upon request from the manufacturing facility. Requiring copies of all supplemental applications to the district office is an additional burden upon both the respondents and the district offices with no benefits for either. This requirement is opposed to the specific goals stated in FDAMA.

   Although AH1 strongly supports deletion of this requirement, at a minimum, the guideline and the proposed rule should be consistent. The rule states "to the appropriate district office." The guideline states "to the applicant's FDA district home office." It is not always clear which office is considered the "home office."

2. Line 98 (and throughout the document) - The term "validate" should be replaced with the term "assess". Validation has a specific meaning under the cGMP regulations. The word "assess" is more appropriate for the context of this document. This comment applies to everywhere the word validate or validation occurs. FDA has attempted to clarify this requirement in the footnote. However, changing the reference to "assess" will help avoid confusion within the industry.

3. Line 189 - The term "sites" needs better definition. FDA has defined "Contiguous Campus" in the glossary, but the term "site" is not included. It is common for industry to consider "site" and "campus" as synonymous. The guide seems to indicate that sites are located within a campus. This implies that moving testing from location within a building or on a campus to another location on that campus as a change of site. For example, changing from one lab to another with the same assay is considered a change of site and must be reported in the annual report. As used in this document, AH1 believes that the term site can be too narrowly interpreted. We suggest that the term "site" be defined to include, at a minimum, designated areas of buildings, such a lab complex, a tableting area or a packaging area. This would allow modifications and movement within these designated areas without a change of site being involved.

3. Lines 353 and 354 (with footnote 8) - The reference to "natural products" should be deleted. There is no there is no basis for differentiating "natural products" from other products where manufacturing changes are concerned. There should be no difference in the regulation or guidance for changes made to natural products or products produced by chemical synthesis.

The requirements for classification of changes should be identical. The reference to "certain production aspects" is too broad and vague. There is no scientific or safety basis to consider veterinary products derived from microorganisms as requiring more stringent requirements. Many products derived from microorganisms, including antibiotics and other products produced from recombinant organisms, have a long history of being produced safely with adequate control of manufacturing changes. The additional requirements placed upon "natural products" will not provide greater assurance of safety or efficacy of these veterinary products. The creation of a significant, new, regulatory hurdle for "natural products" will inhibit innovation in the manufacture of such products. Implementation of separate categorization for natural products is in opposition to the stated goals of FDAMA.

4. Line 393 - Changes to sterilizer load configurations should not be automatically classified as Major changes requiring a prior approval supplement. These changes are validated individually and should be included in annual updates (MCSR). These changes, and the corresponding validation documentation, are maintained at the plant sites for review during field inspections. Requiring submission of all sterilizer load configurations beyond the initial validated limits will require significantly more prior approval supplements without an increased assurance of product sterility. This requirement is opposed to the stated goals of this guideline and FDAMA.

5. Line 408 - Changing from centrifugation to filtration or vice versa should not automatically be classified as a Major change requiring a prior approval supplement. The classification of such a change should be: determined by "the potential for adverse effects on the safety, purity, etc." Not all changes between these technologies have a significant potential for adverse effects. Therefore, this example should be removed.

6. Line 463 and the subsequent paragraph - This paragraph should be deleted. There is no basis for differentiating natural products from chemically synthesized products. The increase in scale during finishing steps with new or different equipment should be evaluated on the basis of the potential for "adverse effects on safety and efficacy". Replacement of equipment with that of similar design should have the same classification as for other products. These changes should be evaluated on the potential for adverse effects. Natural products should not automatically have a higher classification for such changes. As stated earlier, the more stringent requirements stated in this guideline will not provide greater assurance of safety or efficacy of these veterinary products.

7. Line 568 - This sentence should be shortened to stop at the word "compendium." Changes made to comply with compendia1 requirements should be allowed as minor changes. The additional wording in the current proposal implies that prior approval would be required, and possibly rejected, to bring specifications into compliance with a compendia.

8. The guidance document contains neither reference to nor examples for labeling changes. This document should be expanded to address labeling.

August 27, 1999

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

Re: Docket No. 99D-0529; Draft Guidance for Industry on Changes to an Approved NDA or ANDA; Notice of Availability and Request for Comments; Federal Register, Monday, June 28, 1999 (64FR34660); and

Docket No. 99N-0193; Supplements and Other Changes to an Approved Application; Proposed Rule; Federal Register, Monday, June 28, 1999 (64FR34608)

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, healthier and more productive lives. Investing $24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

With the subject proposed rule, FDA is intending to implement the manufacturing changes provisions of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), specifically Section 116 of the Modernization Act which amended the Federal Food, Drug and Cosmetic Act (the act) by adding section 506A which describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to new and abbreviated animal drug applications and to license applications for biological products. The proposed rule would update and replace the current section 3 14.70 of the drug regulations and make changes to section 60 1.12 applicable to licensed biological products.

The draft guidance, according to the Notice issued at the time of the publication

follow:

- "In the past, the FDA has imposed very stringent limitations on the ability of pharmaceutical and biotechnology industries to adopt new manufacturing procedures."

- "The impact of past FDA policy in this area on the pharmaceutical and biotechnology industries has been substantial."

- "To address these problems, the legislation considered by the committee included a new approach to manufacturing changes for new drugs and biological products."

A careful analysis of the June, 1999 proposals shows that, not only is there not significant regulatory relief embodied in these proposals, **these proposals in fact add significant numbers of additional new categories of manufacturing changes for which FDA would require prior approval supplements.** Nor are there new approaches to regulations for manufacturing changes embodied in the proposed new rule and guidance. Approaches such as the Drug Substance and Specified Biotechnology API and Drug Product decision trees forwarded by PhRMA to the agency on November 30, 1998 have not been considered. PhRMA notes that the absence of regulatory relief in the June, 1999 proposals stands in stark contrast with the draft Bulk Active Chemical Postapproval Changes Guidance (BACPAC-I) and the final Postapproval Changes-Analytical Test Laboratories Guidance (PAC-ATLS), both of which have been issued since the FDA Modernization Act do provide significant regulatory relief.

A careful analysis of the new rule vs. existing section 314.70 shows that two new categories of prior approval supplements have been included in the proposed rule:

- 3 14.70(b)(2)(iii) changes that may affect product sterility assurance; and

- 3 14.70(b)(2)(vii) changes solely affecting a natural product.

Neither of these has been explicitly addressed in past rules or guidances. Counterbalancing these are only minor additional possibilities for items that would be reportable in an annual report or submitted as a Changes Being Effected Supplement (CBE).

Given the intent of the FDA Modernization Act, one would have expected the accompanying draft guidance to have included new opportunities for reduced reporting requirements. However this is not the case. Some of the key areas in the guidance include changes such as:

- **sterile processes** - 11 categories for prior approval supplements are described in the guidance;

- **natural (protein) products** – natural products have not been singled out before and three new categories of prior approval supplements are listed in the draft

In addition, the proposed increase in the reporting burden comes despite the specific provision in the FDA Modernization Act for the manufacturer (application, sponsor) to have assessment data regarding the proposed change at the time of the submission of manufacturing change supplements. The FDA Modernization Act specifies that a drug made with a manufacturing change may be distributed only after completing studies that assess the effects of the change (defined as "validation," sec 506a (1)). The legislative intent of the FDA Modernization Act is that if appropriate studies comparing pre- and post-change material are performed and no evidence of an adverse effect is found, then a reduced reporting structure for the evaluated changes is appropriate. The logic for this is inescapable: a given proposed manufacturing change can indeed have substantial potential for adverse effects at its inception, when little might be known about the impacts of the change. However, once actual material has been made with the change and assessment studies have been successfully completed, most or all of the potential impacts of the change have been eliminated. Thus the assessment information showing no adverse effect from the proposed change should permit a reduced reporting requirement under the FDA Modernization Act. This is a critical element of the statutory change enacted by the Congress and signed by the President.

FDA has previously indicated that, in some cases assessment studies have been inadequate'. Et is important to note in this regard that for many post approval changes (e.g., for changes related to sterile processes), the FDA-approved validation of the original process provides an excellent model for how to assess the manufacturing change. In most cases where well designed assessment studies have been completed, the potential for adverse effects is completely eliminated; but in all cases the potential will have been substantially reduced. **Consistent with this reduction of risk it is appropriate that fewer changes should require prior approval supplements under the FDA Modernization Act.**

However, while the "validation" or assessment requirement from the FDA Modernization Act is reflected in the proposed rule and guidance, there is little reduction in reporting requirements and most importantly, no reduction in the requirements for prior approval type supplements that represent the major burden for both industry and the FDA. It is as if the Agency is requiring that the risk assessment be accomplished by the manufacturer, while the Agency continues to assume the worst case risk for any change.

With regard to a new approach to the regulation and management of manufacturing changes, PhRMA recommends a 'decision tree' or 'key questions' approach, that bases regulatory reporting requirements on the results of scientific comparison of pre- and post-change material,as a better approach to guidance. This approach was inherent in the BACPAC-I guidance issued in draft by FDA earlier this year and the Decision Tree for Post-Approval Changes to Drug Products which was developed by PhRMA member companies as a recommended implementation of the FDA Modernization Act provisions and provided to FDA on November 30, 1998. The decision tree approach utilizes some of the learning that went into the SUPAC guidances, but incorporates a different philosophical approach. Consistent with the FDA's Principles for Reforming FDA Regulation under the Reinventing Government

(1) Decision Tree for Bulk Active Post Approval Changes (BACPAC)
(2) Decision Tree for Post Approval Changes to Drug Products
(3) Post Approval Changes to Biological and Specified Biotechnological Active Pharmaceutical Ingredients and Drug Products
(4) Recommended Regulatory Language for Drugs (Small Molecules)
(5) Recommended Regulatory Language for Biologicals (Large Molecules) and Proposed 2 1 CFR 60 1.12 Changes to an Approved Biological/Biotechnological Drug Product Application
Excerpt from Senate Report No. 105-43, Pages 45-46

'Section II of the Guidance for Industry. Changes to an Approved Application: Biological Products. July 1997 and Guidance for Industry. Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, July 1997

[2] "Principles for Reforming FDA Regulation in Carry out this Review," Reinventing Regulation Of Drugs And Medical Devices, National Performance Review, April 1995, Page 4.

PhRMA Comments on:
Proposed Rule "Supplements and Other Changes to an Approved Application" (Docket No. 99N-0193); and
Draft FDA Guidance "Changes to an Approved NDA or ANDA" (Docket No. 99D-0529)
Table of Specific Comments

August 27, 1999

Comments on 21 CFR 314.3

Section	314.3 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Proposed Rule	(b)	496-499; 865-868	Delete "intermediates, raw materials, reagents, and other components including container closure systems and in-process materials." It is recommended that changes for these materials be handled separate from this regulation/guidance.	This definition is not consistent with ICH Q6A, which includes only API and drug product. TO include items beyond the API and DP in this guidance represents a level of complexity that would be better dealt with in later guidances that can adequately evaluate the significance of changes to specific items, including a more in-depth FDA/Industry dialogue. As it currently stands, the guidance attempts to address changes for DP components, DP in-process materials, API final intermediate, starting materials introduced after the final intermediate, starting materials introduced prior to the final intermediate, API intermediate prior to the final intermediate, API in-process materials, API raw materials, reagents, and packaging components versus the following changes: adding a test, deleting a test, adding an analytical procedure, deleting an analytical procedure, changing an analytical procedure, tightening an acceptance criterion, and relaxing an acceptance criterion.

				The result is a confusion of changes, many of which should be noted do not agree with current guidance (e.g., BACPAC).

Comments on 21 CFR 314.70

Section	314.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
roposed Rule	(a)(5)	---	Clarify whether the field copy that is to be sent to the applicant's "home FDA district office" should be the FDA office where the change is being made or the FDA office in the district of the company's corporate headquarters from where the submission documents are sent. Also, if it should be sent to the office where the change is being made, clarify what FDA office (s) serve for changes made internationally (outside the USA).	Clarification will help to ensure that the appropriate documents get to the right FDA district office.
'roposed Rule	(a)(6)	---	Delete "cover letter" and replace with "introduction to the document."	Cover letters (letterhead documents with signatures) are not considered confidential. Recommendation moves this detail to the beginning of the submission.
?roposed Rule	(b)(2)(iii)	370-410; 433-444; 447-465	Delete lines. Replace with "Changes that reduce the sterility assurance level".	The impact on sterility assurance level should be the guiding factor in any change. As proposed, the verbiage is too broad and if interpreted conservatively would be overly burdensome in terms of regulatory reporting.
Proposed Rule	(b)(2)(v)	716	Clarify "labeling.. ." to "drug product labeling.. .".	API labeling changes should not need be submitted to the registration.
Prooosed Rule	(b)(2)(vii);	402-407;	Delete reference to "natural products" and/or	. Clarification reouired on definition of

	:)(2)(ii)	68-473	'natural protein products".	natural product;. Does this include fermentation products? • Having special requirements for this additional category of products represents additional regulatory reporting requirements beyond current practice.
Proposed Rule	b)(3)	--	Add "as appropriate" as follows "Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement, as appropriate".	Not all listed material is relevant for every submission.

Section	314.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Proposed Rule	(b)(3)(viii); (d)(3)(iii)	---	Delete reference to SOPs. Delete "The date each change was made, a cross reference to relevant validation protocols and/or SOPs, and" and the word "(validation)".	This data represents compliance information and is better suited for field inspections. The addition of this information to existing practice would result in increased regulatory burden. The fact that the annual report changes were made during the NDA's annual reportable year should be sufficient information; more specific timing will be available at the manufacturing site in appropriate GMP documentation available for inspection.
Proposed Rule	(b)(4)	62-68	Feedback to Sponsor on acceptance or refusal	Currently the CFR includes the provision for

			of "Expedited Review" Request within 30 days.	"Expedited Review", however, there is no mechanism for communication of acceptance or refusal on expedited review reauest
Proposed Rule	(c)(1)	97-98	Change final sentence to "If the change concerns labeling only, include.. .".	There are changes that have minor impacts on labeling (e.g., signature changes) that, if implemented as stated, would result in increased regulatory burden to provide finished product labeling (FPL) prior to change implementation.
Proposed Rule	(c)(2)(ii)(A)	---	Clarify whether this applies to drug product or API; clarify "finishing steps."	Not clear.

ection	314.70 Regulation Line	Guidance Line Cross-Reference	omment	Rationale
roposed Rule	(c)(2)(ii)(B), d)(2)(iii)	471-473; 481-482	larify equipment that is "similar, but not dentical" versus equipment of the "same design nd operating principal." [Follow Equipment ddendum to various SUPAC Guidances]	Similar/but not identical classifies as a CBE-30, but same design/operating principal is annual reportable; but the difference is not readily apparent. No references under MAJOR changes (Rules) addressing equipment changes, this section may be addressing the "gray" area under SUPAC for equipment of the same operating principle (class) but different design (subclass). The Rule, therefore may have missed the MAJOR change of different operating principle/design that is caught in the Draft Guidance found starting with Line 408. For equipment changes, which are of different operating principle and design – consider Majo category. Changes in equipment which are of the same operating principle but different

				design – consider Moderate change.
Proposed Rule	(c)(6)(ii)	638-639	Add "a sterile drug product, or a sterile drug substance" to read ". . container for a nonsterile drug product, except for solid dosage forms, a sterile drug product, or a sterile drug substance without a change...".	size and shape changes for sterile API and drug products have only moderate potential impact. This is especially true when the nature of the size/shape changes are very minor in nature, as is often the case when suppliers make minute adjustments in their packaging components.
Proposed Rule	(c)(7)	70-73	Replace with "If FDA later determines that the supplemental application is not immediately approvable, the agency will work with the applicant to resolve all issues and to assure the continued availability of the drug."	This is the current practice. Also, this was the intent of the US Senate as recorded in Senate Report 105-43.

ection	3'14.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
roposed Rule	(d)(2)(i)	522-523; 567-57 1	Change to "Any change made to comply with an official compendium."	Section 501(b) of the FD&C Act requires the FDA to resolve any differences with the compendia! body, the USP. It is unfair to place the applicant in the middle of these discussions, and the compendia! review process should be the mechanism via which the FDA has influence. In addition, it should be permitted and appropriate that any USP-adopted changes, including changes that may relax acceptance criteria and/or analytical procedures, be updated via an annual report. Such an updated process would apply to both the innovator as well as any generic companies.
Proposed Rule	(d)(2)(iv)	561-662	Delete "containing the same number of dosage	For nonsterile solid dosage forms, the fill count

			nits".	of the bottle should be allowed to be changed along with the size/shape. The current verbiage would allow size of the bottle to increase (and therefore more headspace) but the fill count to not equivalently change.
Proposed Rule	(d)(2)(viii)	*85-487*	Revise to: "The addition by . . ., or an addition or change in an ink imprint".	Per 21CFR 206 (Imprinting Of Solid Oral Dosage Form Drug Products For Human Use) which has been in effect for over 5 years, al! solid dosage forms are required to have imprints. Therefore, "to add an ink code imprint" as drafted applies to changing from-embossing/debossing/engraving to ink iimprinting.
Proposed Rule	(d)(2)(x)	*165*	Add " . . . a distributors name *or editorial changes to comply with an official compendium.*"	Consistent with current practice, changes to comply with the USP (e.g., official USP titles) should remain annual reportable.
Throughout the proposed rule and guidance			Clarify and standardize use of "drug product," "drug," and "product." Change "drug substance" to "active pharmaceutical ingredient" to be consistent with other guidances. Clarify if "product" includes API or not.	Terminology changes throughout the document can lead to confusion of interpretation.

Section	314.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Throughout the proposed rule and guidance	---	---	The term "validate" is likely to cause confusion with the cGMP concepts of validation. Though explicitly used in FDAMA, it would be best to avoid or continually clarify "validate" in the context of 506A. Suggest verbiage change to "assess the impact of the change."	Validation (cGMP) has specific meaning within the industry. Confusion will result if the same term is used. The recommended verbiage better describes the intended action.

Comments on the Guidance "Changes to an Approved NDA or ANDA"

ection	Guidance Line	114.70 Regulation Line Cross-Reference	Comment	Rationale
'hroughout the roposed rule and uidance	--	---	Clarify and standardize use of "drug product," "drug," and "product." Change "drug substance" to "active pharmaceutical ingredient" to be consistent with other guidances. Clarify if "product" includes API or not.	Terminology changes throughout the document can lead to confusion of interpretation.
Throughout the roposed rule and uidance		---	The term "validate" is likely to cause confusion with the cGMP concepts of validation. Though explicitly used in FDAMA, it would be best to avoid or continually clarify "validate" in the context of 506A. Suggest verbiage change to "assess the impact of the change."	Validation (cGMP) has specific meaning within the industry. Confusion will result if the same term is used. The recommended verbiage better describes the intended action.
I. Introduction	19-22	---	The changes to biotech products should be updated contemporarily with this guidance as well as both are covered under FDAMA.	Guidance is from before FDAMA, and this might suggest that the Agency is codifying prior initiatives and not actively looking towards revising the 7-97 biotech guidance as per FDAMA.
Same	34	---	Agency should delete "in such prior guidance … by this guidance" and add "shall be the least burdensome".	FDAMA was intended to decrease the overall reporting requirement,
II. Reporting	41-84	---	None of the definitions truly define what the	Note: FDAMA places the burden upon the

categories			Agency views as "substantial potential", "moderate potential", and" minimal potential" to have an adverse effect on the identity, quality, purity, or potency of the product.	Agency to show that changes other than those specifically noted in FDAMA (e.g., change in composition and changes needing clinical/bioequivalence evaluation) have a reasonably high likelihood to adversely affect the product.
Same	54-56	---	The Guidance should expand on those areas of hardship based on unforeseeable circumstances that may necessitate expedited review.	Catastrophic circumstances is too limiting. There are other situations beyond the applicant's control where the Agency could partner with the applicant to assure continued supply to the patient.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
Same	64-68	(b)(4)	FDA should identify time limits for review of an applicant's response to a notification within the 30 day window.	if the review time is left unspecified, then it effectively becomes PA supplement, just because more information is requested. Suggest if response is within the 30 day window, FDA should stick to original 30 day limit. If response comes in afterward, then another 30 day window is established. This would be similar to the IND review process during the 30 day wait period.
Same	72-73	(c)(7)	Must be clarified that non-approval for reasons other than circumstances that may obviously impact safety or efficacy (e.g., not simple information requests) is not justification to halt distribution.	This is a major action that should be strongly justified.
Same	79-84	---	Commend the Agency for capturing the change protocol concept for all drugs from that originally developed for biotech products.	The comparability protocol concept can usefully be applied to non-biotechs also.
III. General Requirements	89	(a)(6)	For annual reports this section should refer to a summary introduction of the CMC section instead of a cover letter.	There presently is no requirement for a cover letter to an annual report under 3 14.81.

Lame	97-100	---	Move this information to "X. Labeling."	These comments are specific to labeling issues and might be better understood in the labeling section.
Same	101	(a)(5)	Clarify Field copy requirements for foreign sites.	Do not have home district for foreign sites.
V. Assessing the Effect of Manufacturing Changes; A. Validate the Effects of the Change	105, 154, 167	---	Format change: Delete line 105, and change lines 154 and 167 to "3" and "4", respectively.	The revised format is Clearer.
Same	111	(a)(1)	Insert "summaries of' in front of "information developed by the applicant".	Summaries of the data collected for a change should be sufficient for describing the evaluation conducted by the applicant in assessing the change.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
2!. Additional Testing	129	---	Additional testing should be clarified in Guidances including a microbiological guidance.	The examples appear to cite those examples where a great deal of data is needed, and those circumstances are in reality rather rare. Must be sure they do not become the norm.
IB. Equivalence	155-157	---	Change "of the drug product" to "of the material produced at the processing step where the change is made or at a subsequent step."	Equivalence is demonstrated at the processing step where the change is made or at a subsequent step. According to BAPAC I, equivalence may be demonstrated at a drug substance intermediate, and does not require assessment of the drug product.
V. Components	187-194	(d)(2)(viii)	Add reference to 2 1 CFR 3 14.70(d)(2)(viii), with	Per 21CFR 206 (Imprinting Of Solid Oral

nd Composition			appropriate modifications to 21 CFR 314.70(d)(2)(viii) as suggested in the PhRMA comment for guidance lines 485-487 (below).	Dosage Form Drug Products For Human Use), which has been in effect for over 5 years, all solid dosage forms are required to have imprints. Therefore, "to add an ink code imprint" (lines 185-487) applies to changing from embossing/debossing/engraving to ink imprinting. Addition of imprinting ink will be an annual report requiring submission of new components and composition sections to the NDA.
VI. Sites 4. General Considerations	197-340	---	Four terms (site, facility, campus and establishment) are used throughout this section. A definition in the glossary is provided only for contiguous campus.	Appropriate simplification of reporting requirements would make these distinctions unnecessary.
Same	200	---	Insert "primary" in front of "packaging" to read "primary packaging materials".	Listing control laboratories for secondary packaging components represents an increased regulatory burden.
Same	211-221	---	Delete lines 2 1 l-22 1	Duplication of information already provided in lines 248-261

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
Same; El. Major Changes	213-215; 250-252	—	Recommend striking point (2) on discontinuation of operation; Also delete lines 250-252 beginning "or the type of operation being moved used to be performed.. .."	The driver here should be a satisfactory cGMP inspection for the type of operation in question. With current verbiage (manufacture was discontinued at some time) confusion will result from real-life situations (e.g., campaigned products). Whether or not a type of operation has been stopped and is now being restarted should not be the deciding point; instead, whether or not the facility has a satisfactory cGMP inspection for the type of operation in question is the key . There may often be quite a time gap between manufacturing campaigns for low volume products.

iame	236-237; 264	b)(2)(vi)	Change "(or modify) the dose delivered to the patient" to "control the release of the active pharmaceutical ingredient",	Current verbiage is not clear or complete in hought.
Same	238	---	Delete "aseptic processing" and substitute MDI, DPI, etc..	This verbiage could imply that any site change For an aseptic operation is a major change (i.e., prior approval supplement). As the guidance later clarifies that some aseptic processing site changes are not major (e.g., moves on the same campus or within a single facility), this wording presents potential confusion.
VI. Sites B. Major Changes	248-249	---	Add "or to label a drug product" as follows: "A move to any site, except one used to manufacture or process a drug substance intermediate or to label a drug product, . . ."	Any drug product labeling facility is required to have the appropriate cGMP compliance practices of segregation of materials, identification of product components, and traceability. The requirement of a prior approval submission for a labeling operation provides additional regulatory burden but carries minimal product risk. A Supplement-Changes Being Effected in 30 days would allow the appropriate FDA inspection without lengthening the industry implementation timeline.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
Same	256-262	---	Clarify the difference between different site and a site on a different campus.	Clarification will assist in consistent interpretation.
Same	259-260	---	Delete "(2) changes that could affect Contamination.."	This example represents a GMP compliance issue that should be regulated by the field.
Same	262-269	---	Add sentence "Once this change.. . . . .in 30 days" (lines 273 -276) to this paragraph.	Treat all dosage forms as similar so that CBE supplements can be submitted for site transfers once the original site transfer is approved.
Same	266-267 ,	---	, Strike "modified release solid oral dosage forms"	, The actual site will have minimal impact on the

			From Major category and add to Moderate (CBE-30).	ıerformance of the product characteristics as ıresented within site specific stability argument – he real issue is the process validation, not the ıite
;ame	2[illegible]-2[illegible]9	---	We would suggest a depot formulation as an example of modified-release parenteral site changes that would fall into this category.	N/A
iame	27 l-276	---	Move "refurbished" and "different aseptic processing facility" to CBE-30. (Keep "newly constructed" as prior approval for the first product).	The ability to move parenteral operations ɔetween different manufacturing facilities which ıave a satisfactory parenteral cGMP inspection should represent no additional regulatory burden ɔver that for non-sterile products.
Same	272	I---	Insert "aseptically processed" in front of "sterile drug product".	Clarification that this phrase applies to both the drug substance and drug product
Same	274-275	---	Define or clarify "similar product types and processes". Consider providing examples.	Verbiage is not clear; examples of differences would be solutions versus suspensions versus freeze dried versus lyophilized powder-filled products.
Same	277-279	---	Verbiage is confusing "Except for modified release solid oral dosage form products, a move to a site on a different campus for primary packaging of a drug product that falls within the scope of examples 4 and 5 (above)." The "except" and "examples" clauses are confusing.	Verbiage is somewhat circular and confusing.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
VI. Sites C. Moderate	284	---	Add example: "A move of drug product labeling to a site on the same campus, when the new	The cGMP compliance practices present in the existing facility would be easily transferred to the

Changes			facility has never been inspected by the FDA for drug product labeling."	new facility, and the drug product labeling operation represents minimal product risk. The 30-day effectivity provides FDA the time to complete a compliance inspection of the new facility, if necessary, without unnecessary delay of implementation by the applicant.
Same	285-291	--	A move to a site on a different campus or changes within a single facility or same campus for the manufacture of drug substances or drug product should be reported within an annual report.	Since the requirement for a satisfactory cGMP inspection will have already been met, the process is not changing, and FDAMA requires prior 'validation', such changes represent minimal risk and should be annual reportable.
Same	303-309	---	Delete "same or". Only a move to a different campus should require a Changes Being Effected Supplement.	A non-sterile drug product may be moved within the same site (i.e., building change) in an annual report (see lines 319-322). To require a Changes Being Effected Supplement for drug substance intermediate is excessive.
VI. Sites D. Minor Changes	317	---	Delete sentence.	Currently, locations of testing sites within a laboratory are not identified. New testing site could be to a adjacent laboratory bench which should not require annual report notification.
Same	333-334		Modify example to "Change in the floor plan which results from a facility "build out."" Move example under example "4."	Change in verbiage eliminates unnecessary reporting of insignificant changes to floor plans and concentrates on facility build out. Currently, room location or floor plans are not identified in registrations. The proposed verbiage would require that continuous GMP improvements be reported, adding additional reporting burden. Format change would flow better after the example for same campus changes.
Same	335-336	---	Delete example "Improvements to manufacturing areas that provide greater assurance of quality."	This example represents a GMP compliance issue that should be regulated by the field if at all.

Section	Guidance	314.70	Comment	Rationale

	Line	Regulation Line Cross-Reference		
VII. Manufacturing Process 4. General Considerations	347-351; 591-595	---	Delete these lines. Inference is that the applicant is not able to adequately evaluate the potential adverse effects of a change.	The burden of risk falls on the applicant to appropriately validate the effects of the change. The applicant has the most first-hand knowledge of the issues for a product/process, and per the original validation work included in the initial (A)NDA, should be granted the scientific technical ability to evaluate the change. In cases where applicants have demonstrated a lack of technical ability, special remedies should be sought rather than penalizing all firms.
Same	357	(b)(2)(iii)	Delete or narrow the phrase "(2) changes may affect product sterility assurance".	Statement is too broadly worded and similar to lines 370-401; 433-444, and 447-465 could be interpreted to suggest an overly burdensome level of additional regulatory reporting requirements.
VII. Manufacturing Process B. Major Changes	361-491; 517-520	---	Clarify if these sections are meant to apply to API and/or drug product. Examples: Lines 408-414 include what appear to be both API and drug product examples, but lines 415-420 are specific to API; Lines 468-473 are not clear as to whether API or drug product is covered.	Confusion will result otherwise.
Same	368-369	(d)(2)(viii)	Addition of embossing, debossing or engraving on a modified release solid oral dosage form may not have substantial potential for adverse effects and is readily assessed by the approved multipoint dissolution test.	The exception should not become a rule, This should not be a major change.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
Same	370-401;	(b)(2)(iii)	Delete all lines. The list of changes that may	The list of sterile process/product changes

	33-444; 147-465		affect product sterility assurance is overly extensive and not appropriate for this general guidance. (1) Changes in many of these criteria should be maintained as cGMP documentation at the manufacturing sites and available for inspection by the agency. For example, changes in equipment (lines 380-383), changes in sterilizer load configurations (lines 398-399), changes in dry heat depyrogenation systems (lines 435-437), changes to filtration parameters (lines 438-444) are all cGMP issues that should be covered during compliance inspections. (2) Add "Changes that reduce the sterility assurance level." in place of lines 370-401. (3) Add "Changes that provide the same or better sterility assurance level." in place of lines 433-444 and lines 447-465. A good example of a change providing better assurance is the replacement of an aseptic fill area with an isolator system. (4) Add bullet for "Change from sterile filtered or aseptic processing to terminal sterilization, or vice versa." after line 4 14.	present an overly burdensome level of additional regulatory reporting. (1) For many of the changes, the appropriate cGMP documentation of the impact on sterility assurance may be more quickly evaluated by compliance specialists in the field than by causing an implementation delay with submission preparation and approval. (2 and 3) The impact on the sterility assurance level (SAL) should be the guiding factor in any change. If the change reduces SAL, a prior approval submission is warranted. A lower reporting level (e.g., CBE-30) should be permissible if the applicant has adequately validated the process and shown that the change provides an equivalent or better SAL. (4) This type of major manufacturing change represents a good example of a fundamental change in the manufacturing process or technology for a parenteral drug product.
Same	402- 407; 468-473	(b)(2)(vii) (c)(2)(ii)	Delete these requirements for natural products.	These new requirements add additional regulatory burden from that of current reporting requirements without expressed justification or definition.
Same	408	---	Clarify the phrase "Any fundamental change in the manufacturing process". The phrase is too vague and all-encompassing, even with the examples provided. Also consider providing parenteral examples.	The broad scope of the verbiage will lead to confusion.

Section	Guidance	1314.70	Comment	Rationale

	Line	Regulation ine 'ross-Reference		
me	)8-409	--	Delete the phrase "which is currently used by the applicant" and substitute "which is currently approved" .	This phrase is confusing. Changes to processing or technology are relevant with respect to a given drug product or API rather than to whether they are "used by the applicant" which could be construed to apply across families of products or different APIs.
ame	1 l-412	--	Delete this example.	This example is not sufficiently defined. The example presented is only a change of equipment principles within the unit operation of drying.
ame	13	--	Clarify that 4 13 applies only to drug products and not APIs.	N/A
ame	1	--	Delete.	Detailed under lines 4 15 – 420.
ame	16-420	--	Replace the examples given with the following • A change in drying or milling equipment only if all three of the following criteria are met: 1) Equipment is of a different design and operating principle. 2) Equipment used after the last true solution. Example: If a solution of the drug substance is prepared in the drug product process, then this criterion is NOT met. 3) Physical characteristics are important in drug product performance. Example: Physical characteristics are important to a low permeability, low solubility drug substance used in a solid oral dosage form.	Existing verbiage is far too general and is confusing when compared to lines 43 l-432. It also presupposes matters better discussed as part of BACPAC – II. Changes in scale or processing parameters from a final intermediate to the drug substance do not warrant a prior approval supplement, assuming that the applicant has assessed the change and shown material before and after the change to be equivalent. Other equipment changes after the final intermediate processing step are unlikely to affect the quality of the bulk drug substance, and therefore, requiring a prior approval supplement presents additional regulatory burden. A change in process is a change in solvents, reagents, process parameters or purification procedures (Reference: BACPAC I), Bulk drug substance process changes are most likely to result in changed impurity profiles; the guiding principle is that the change must be assessed, and material before and after the change must be equivalent. Examples: Change in solvent or reagents (prior approval); change a process parameter In g., temperature, pH, stoichiometry

			• A new or different solvent and/or reagent after the final intermediate processing step. • For an API, a change in the route of synthesis involving different intermediates.	parameter (e.g., temperature, pH, stoichiometry, time) (tighten - annual report)(widen – CBE30).

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
VII. Manufacturing Process C. Moderate Changes	413 1-432	--	Replace the existing text with the following: For drug substance, • Change in scale (>2x) in the final *step* of the synthesis. • Change in drying or milling equipment only if all three of the following criteria are met: 1) Equipment is of a different design and operating principle. 2) Equipment used after the last true solution. <u>Example</u>: If a solution of the drug substance is prepared in the drug product process, then this criterion is NOT met. 3) Physical characteristics are NOT	As proposed, all process/process parameter and/or equipment changes that are not listed as prior approval or annual reportable would defaul t o CBE supplement. This would result in an ncreased regulatory burden. The guiding principle is that the change must be assessed, and material before and after the change must be equivalent. These aspects of bulk changes would be better detailed in the appropriate BACPAC documents.

			important in drug product performance. • Widen a change in process parameter ranges (e.g. temperature, pH, stoichiometry and time) after the final intermediate processing step • A new or different solvent and/or reagent before or during the final intermediate processing step.	
Same	445-446		This is a good example of a change that should require a CBE-30 submission, as it causes a change in the NDA process description.	N/A
Same	474	---	Recommend adding example for API: • Routinely repeating a purification step already in the application for steps after the final intermediate processing step.	No examples provided.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
VII. Manufacturing Process D. Minor Changes	176-491	--	Recommend adding examples for API: • Change in scale (≤5X) for all steps prior to the final *step*. • Change in scale (≤2x) for the final step • Tighten an in-process parameter range (e.g., temperature, pH, stoichiometry, time) for all API process steps.	No API examples are provided in this section.

			• Widen an in-process parameter range (e.g. temperature, pH, stoichiometry, time) for steps prior to and including the formation of the final intermediate. • Change in equipment to that of a different design and operating principle, except changes in drying and milling equipment requiring a supplement. Routinely repeating a purification step already in the application for steps before and including the final intermediate processing step.	
Same	485-487	(d)(2)(viii)	Revise this line to state "To change from an embossing/debossing/engraving imprint to ink imprint or change in.. .."	Per 21CFR 206 (Imprinting Of Solid Oral Dosage Form Drug Products For Human Use) which has been in effect for over 5 years, all solid dosage forms are required to have imprints. Therefore, "to add an ink code imprint" as drafted applies to changing from embossing/debossing/engraving to ink imprinting.
Same	4 9 1	---	Add "or lyophilized" dosage forms.	Change in order of addition of ingredients for lyophilized dosage forms should have no different impact than solution dosage forms.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
VIII. Specifications A. General	496-499; 865-868 117-123;	314.3(b)	Delete "intermediates, raw materials, reagents, and other components including container closure systems and in-process materials." It is	This definition is not consistent with ICH Q6A, whicih includes only API and drug product. To include items beyond the API and DP in this

lonsiderations	22-524; 40-556; 78-583		ecommended that changes for these materials be ıandled separate from this regulation/guidance. Delete these examples as they also refer to the ıbove-listed items.	guidance represents a level of complexity that would be better dealt with in later guidances that can adequately evaluate the significance of changes to specific items, including a more in-depth FDA/Industry dialogue. As it currently stands, the guidance attempts to address changes For DP components, DP in-process materials, API final intermediate, starting materials introduced after the final intermediate, starting materials introduced prior to the final intermediate, API intermediate prior to the final intermediate, API in-process materials, API raw materials, reagents, and packaging components versus the following changes: adding a test, deleting a test, adding an analytical procedure, deleting an analytical procedure, changing an analytical procedure, tightening an acceptance criterion, and relaxing an acceptance criterion. The result is a confusion of changes, many of which should be noted do not agree with current guidance (e.g., BACPAC).
Same	501-504	---	Clarify that production environmental controls (e.g., environmental monitoring for particulates and/or microorganisms) are GMP in nature and not specifications requiring regulatory submissions.	Although provided initially in registrations via the sterilization validation package, these production controls are considered GMP in nature and should be handled via FDA Compliance.
VIII. Specifications B. Major Changes	519	---	Rephrase as "Replacing a current regulatory analytical procedure or establishing a new regulatory analytical procedure".	The proposed revised text covers both options
Same	530-53 1	---	Change to "(3) one that distinguishes impurities but the limit of detection is higher and greater than 0.1% and/or limit of quantitation is higher."	Change makes this phrase consistent with ICH limits of detection.

I Section	Guidance 1314.70	Comment	Rationale

	Line	Regulation Line Cross-Reference		
VIII. Specifications C. Moderate Changes	538	---	Change to "Any changes in a regulatory analytical procedure for which the change significantly impacts the method validation package." Also change this example to CBE versus CBE-30.	• Minor revisions are often made in regulatory analytical procedures (e.g., typographical corrections, clarifications, analyst safety precautions). • Development of a good AM-FAC guidance would be the best way forward here.
Same	558	---	Revise to "An addition to a specification or changes in analytical procedures and acceptance criteria for the drug substance or the drug product to provide increased assurance of identity, strength, quality, purity or potency."	The suggested verbiage is consistent with the other parts of the regulation and guidance.
VIII. Specifications D. Minor Changes	567-57 1	(d)(2)(i)	Change to "Any change made to comply with an official compendium."	Section 501(b) of the FD&C Act requires the FDA to resolve any differences with the compendia1 body, the USP. It is unfair to place the applicant in the middle of these discussions, and the compendia1 review process should be the mechanism via which the FDA has influence. In addition, it should be permitted and appropriate that any USP-adopted changes, including changes that may relax acceptance criteria and/or analytical procedures, be updated via an annual report. Such an updated process would apply to both the innovator as well as any generic companies.
Same	573-576	---	Delete "that provides.. ..in the approved application."	For alternative analytical procedures, the applicant carries the burden of proving that it provides the same or greater level of control. Therefore this phrase is more of a definition of the term and is thus redundant.
Same	584-585;	---	Delete these examples of specifications for	Reference standard information is included in

	794-799		reference standards and updating of reference standards.	initial NDA submissions but is not routinely updated after the initial approval. This proposal would represents and additional regulatory reporting burden.

ection	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
X. Package 1. General Considerations	586-713	---	This section categorizes packaging changes based on providing examples of very specific changes for the various dosage forms. While the examples cover many of the changes typically needed from a post approval perspective, they fall short and as technology and processes improve, the guidance will quickly become outdated. Changes should be categorized based on the potential for interaction with DP and change in the protective properties of the container/closure system in context of the dosage form.	Packaging changes are often the most scientifically straightforward of pharmaceutical changes. Decision trees based on drug product Interaction and container/closure protective properties provide a science-based approach to regulatory change assessment. The examples proposed represent an increase in the regulatory burden for packaging post approval changes in some areas and reduction in others. There is a very obvious disconnect in the approach of this guidance and the Packaging Guidance recently issued.
Same	596-606	---	All these listings are redundant with the examples that follow on lines 612-641.	Unnecessary duplication may lead to inconsistencies over time.
IX. Package B. Major Changes	616	---	Clarify example "(1)," specifically the phrase "with that particular liquid dosage form". Does "particular dosage form" imply product family (e.g., cephalexin) or dosage type (e.g., solutions, suspensions) or both?	Wording is unclear.
Same	619-621	---	For liquid (e.g., ---------) and semisolid (e.g., -------), where ink -----.	Restructure sentence for clarity and provide examples.
Same	638-639	---	Move to Supplement – Changes Being Effected in 30 days.	size and shape changes for sterile API and drug products have only moderate potential impact. This is specially true when the nature of the size/shape changes are very minor in nature, as is often the case when suppliers make minute adjustments in their packaging components.

Same	640-641	---	Clarify what is meant by "additional protection".	Examples could be provided with regard to what are the essential variables (e.g. light, moisture).
IX. Package C. Moderate Changes	647	---	Delete "secondary".	A change in secondary packaging components is listed as CBE 30 days. These components are generally cartons and are not specified in the NDA. Therefore, should not be the subject of a supplement.
IX. Package D. Minor Changes	653	---	Add example of parenteral changes, such as "Change in the flip seal (color, cautions) not impacting labeling."	There are no parenteral packaging examples provided.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
Same	653	---	Add "A change in a vendor without any other major changes in the packaging component."	A change from one vendor to another making the same essential packaging component should be annual reportable.
Same	653	---	Since the glossary (definition of "package") mentions dosing cups, droppers and spoons, discussion of adding or deleting such components to the package is recommended.	N/A
Same	661-662	(d)(2)(iv)	Delete "containing the same number of dosage units".	For nonsterile solid dosage forms, the fill **count** of the bottle should be allowed to be changed along with the size/shape. The current verbiage would allow size of the bottle to increase (and therefore more headspace) but the fill count to not equivalently change.
Same	666-667; 681-682	---	Clarify CDER-approved solid oral dosage form products.	If a list of CDER-approved solid oral dosage form products exist, it should be published.
Same	672-673	---	Change to "Changes in packaging materials used	The clarification details the extent of the example

			to control odor (e.g., charcoal packets) or' moisture (e.g., desiccants). This includes changes to both the agent (e.g., charcoal, silica) and the packet (e.g., canister).	and adds desiccants as an equivalent packaging change. The introduction verbiage still requires the desiccant to provide the same or better protective properties.
Same	676	---	Change "Increasing" to "Changing".	Increasing or decreasing the wall thickness should be annual reportable if the container provides the same (or better) protective properties as required by the verbiage in the introductory information.
Same	679	---	Add "colorant" to "A change in an antioxidant, colorant, stabilizer.. .".	Colorants are similar in nature to antioxidants and stabilizers in resin formulations.
Same	683-684; 687	---	Nonsterile liquid and semisolid dosage form products	Consistent terminology should be maintained. ("nonsterile")
Same	685-687; 699-700	---	Clarify CDER-approved liquid oral or topical dosage form products.	If a list of CDER-approved liquid oral or topical dosage form products exist, it should be published.
Same	711-713	---	Delete this example.	Detail on secondary packaging components that are not intended to provide additional protection to the drug product represents additional regulatory burden and should not need to be maintained in a submission.

Section	Guidance Line	314.70 Regulation Line Cross-Reference	Comment	Rationale
X. Labeling	717	---	Some guidelines around the requirement to "PROMPTLY revise all promotional labeling" might be helpful. For example, (consistent with past FDA practice) significant safety or efficacy revisions should be made within 30 days, less significant revisions within 60-90 days. Minor revisions at the time of the next printing.	N/A
Same	736-7	---	Change 7. to "Change to a less restrictive labeled	Changes to more restrictive storage conditions,

			storage condition, unless exempted by regulation or guidance."	should not require prior approval.
Same	'65	d)(2)(x)	Add " . . . a distributors name *or editorial changes to comply with an official compendium.*"	Consistent with current practice, changes to comply with the USP (e.g., official USP titles) should remain annual reportable.
Same	167	--	Add: 4. Adoption of Uniform Storage Statements (USSs).	As per FDA's draft stability guidance.
XI. Miscellaneous A. Major Changes	781	--	Delete "or based on pilot scale batch data."	Since ICH (ICH Q1A), the FDA draft Stability Guidance and FDAMA allow for the establishment of the original expiration date based on pilot scale data, extending dating based on these same batches does not seem to represent a substantial risk to safety or efficacy, providing that a suitable protocol has been agreed upon (i.e. approved in the NDA).
XI. Miscellaneous B. Moderate Changes	785	---	Add: A reduction of expiration dating in order to provide assurance that the drug product will meet all quality specifications over its shelf-life.	If the drug product's ability to meet specifications over its shelf-life is in question, increased assurance can be gained by a reduction in dating (and such changes should not be delayed by requiring submission of a prior approval supplement).

Section	**Guidance Line**	**314.70 Regulation Line Cross-Reference**	**Comment**	**Rationale**
XI. Miscellaneous C. Minor Changes	793	---	Revise to: "Revision of the approved stability protocol by addition of time points or tests, or by deletion of certain time points after a significant body of data has been collected and the deletion is in accord with provisions made in the original NDA, or by deletion of time points beyond the	Adding a test or a time point to a stability protocol must be permitted in the annual report, as this provides "added" assurance. Also, with mature products (having collected a "significant body of data"), there is little value in certain time points (e.g., 3 and 9 months) and deletion of

			ıpproved expiration dating period."	hese in accord with approved provisions in the NDA must be allowable in the Annual Report. nitial registrations may also have time points isted beyond the expiry period to show that the applicant may evaluate these time points for potential dating extension. Once this data has nen collected, if the applicant does not wish to continue to test these "extra" time points, this example would allow the protocol to be appropriately updated.
XII. Multiple Changes	305	--	Add: ". . .individual changes. For example, multiple changes having the same reporting level, that same reporting level will apply to the cumulative changes. "	This has been a contentious issue on occasion and should be clarified.
Glossary of Terms	306	---	Add definitions for "Comparability Protocol," "Campus", "Site", "Facility," and "Establishment", as appropriate.	If these terms remain in the guidance they need to be well defined in the glossary.
Same	325-829	---	Add: . , . "covalent bond formation *or breakage".*	Breaking covalent bonds is a significant chemica change that should differentiate the final intermediate from the drug substance. This comment was also made to BACPAC I.
Same	851	---	Add: . ". . , . *is an inspection (either cGMP or PAI for the appropriate operation or dosage form)* during which.. . ..". It is also unclear whether the conspicuous absence of the "within the past two years" criterion was deliberate and is no longer applicable.	It is burdensome not to allow a satisfactory PA1 for a given type of operation or a given dosage form to represent a satisfactory cGMP inspection.
Same	863-4	---	This definition allows for two classes of secondary packaging components: Protective and non-protective. While this guidance attempts to maintain the distinction, there is some opportunity for confusion. It is time to consider moving away from these frequently misused or misleading terms.	N/A