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September 23, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-D-0283: Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports." BIO welcomes FDA's initiative to apply scientific and risk based principles to reclassify changes as annual reportable. We encourage the Agency to consolidate existing Chemistry, Manufacturing, and Controls (CMC) reporting guidances, clarify how CMC reporting for biologics will be addressed under future guidance, and help reduce the potential for unintended consequences that may inadvertently increase the regulatory reporting burden.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

1. Consolidation of Guidance Documents Can Minimize Inconsistencies

There are multiple final FDA guidances that provide recommendations for how the Agency wishes to be notified of post approval CMC changes. Further, some of the changes described in the current Draft Guidance are already included in the existing "Changes to an Approved NDA or ANDA" guidance. Yet, on the other hand, some of the annual reportable changes described in the "Changes to an Approved NDA or ANDA" guidance are not contained in the current Draft Guidance, such as a move to a different manufacturing site for secondary packaging or labeling. The reasons for this inconsistency are unclear, as are the reasons for having multiple guidances on these topics. To avoid the confusion likely to stem from the availability of multiple guidances that cover the same topics, we recommend that these guidances, including the various "Changes to an Approved NDA or ANDA" and Scale-Up and Post-Approval Changes (SUPAC) guidances, be consolidated as appropriate and as soon as possible. If FDA does consolidate the guidances, please consider the format adopted by Health Canada in its guidance entitled, "Post-Notice of Compliance Changes: Quality Document." This guidance, in addition to consolidation of advice on post-approval manufacturing changes into a single document, clearly demonstrates how understanding CMC manufacturing changes and supporting data can result in regulatory relief.[1]

2. Reporting Requirements for Biologics Should Be Clarified

We also note that the scope of the guidance as written covers New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), but does not discuss biologics regulated under Biologic Licensing Applications (BLAs). We encourage the Agency to extend its work and identify low risk changes to biologics governed under a BLA that are suitable for reporting in an annual report. In fact, many of the principles and changes suggested under the guidance are broadly applicable to biologic products (*1.1, 1.3, 2.1-2.3, 3.2-3.8, 4.1-4.5, 4.10, 4.11, 5.2, 5.4, 5.5, 6.1, and 6.2*). For example, the risk profiles of the proposed changes are identical and not related to the registration process. As products registered under all of the listed processes have similar (and often identical) annual reporting requirements, the changes listed may be applicable to these additional products.

BIO requests that FDA clarify the status of reporting requirements for biologic products. This could be accomplished by explicitly stating in the "Introduction" to the Draft Guidance that:

1. Biologics subject to Sec. 351 of the Public Health Services Act are not covered under the scope of this guidance and continue to be subject to reporting requirement under 21 CFR 601.12 and existing applicable guidance; and
2. Risk-based principles to reduce the reporting burden for biologics will be addressed in a forthcoming CBER/CDER guidance or revisions to existing guidance.

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1 Health Canada, Post-Notice of Compliance (NOC) Changes: Quality Document, September 2009, http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.pdf,

3. Some Provisions May Have the Unintended Effect of Increasing the Regulatory Burden

The Draft Guidance recommends that CMC annual reportable changes be supported by (among other things) "cross references to validation protocols and standard operating procedures and policies" (line 131). These documents are frequently updated and revised. Currently, except for certain specific categories of products (i.e., natural products, recombinant DNA-derived proteins/polypeptides, complexes or conjugates of a drug substance with a monoclonal antibody), GMP/Compliance regulations require this information to be kept on file and presented to FDA upon request (for example, during an inspection). We are concerned that this general recommendation has the potential to increase industry's regulatory reporting burden. We recommend modifying the recommendation to include a reference to reflect the regulatory requirement as stated at 21 CFR 314.70(d)(3)(v).

CONCLUSION:

BIO appreciates this opportunity to comment on "Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports." We have provided more specific comments in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	PROVISION	PROPOSED CHANGE
I & II. INTRODUCTION & BACKGROUND		
Lines 17-18:	"This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes that may be reported in annual reports. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely present minimal potential to have adverse effects on product quality and, therefore, may be reported by applicants in an annual report."	While many of the principles of the guidance apply to biologics, it is unclear how biologics subject to Sec. 351 of will be treated under this guidance or whether they may be addressed in future guidance. BIO requests that FDA clarify the status of reporting requirements for biologic products. This could be accomplished by explicitly stating in the "Introduction" that: **1.** Biologics subject to Sec. 351 of the Public Health Services Act are not covered under the scope of this guidance and continue to be subject to reporting requirement under 21 CFR 601.12 and existing applicable guidance; and **2.** Risk-based principles to reduce the reporting burden for biologics will be addressed in a forthcoming CBER/CDER guidance or revisions to existing guidance.
1.3	"New supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged."	These lines provide for reporting a new supplier of an inactive ingredient for a drug product in the annual report. However, often suppliers of excipients are not specified in the NDA. The January 2001 Q&A document for Changes to an Approved NDA or ANDA states that a change to a different manufacturing site for an excipient does not require notification to CDER. Requiring this change to be reported in an annual report could lead to an increase in reporting requirements. Please revise item 1.3 as follows:

		"Where specified, a new supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged."
1. Manufacturing Sites		
2.1	"Modification of an approved manufacturing facility that does not affect a product manufacturing area or sterility assurance and does not change product quality or specifications."	Please clarify that if the quality of drug substance or drug product will unlikely be negatively impacted if tested by a new testing lab site, then it would be considered an annual reportable change. For example, if a testing lab is added to perform testing as per the currently approved specifications for either drug substance or drug product, there are no changes to the approved validated analytical procedures or acceptance criteria, the testing site has obtained a satisfactory Agency inspection within the last two years, and the method transfer activities have taken place, then the quality of drug substance or drug product will unlikely to be negatively impacted if tested by the new site. Would this be considered an annual reportable change?
2.4 *(proposed)*	N/A	Please also add deletion of a manufacturing or testing site as a change that can be annual reportable by including the following bullet at the end of section 2: " 2.4. Deletion of a manufacturing or testing site"
2. Manufacturing Process		
3.1	"Process changes including any of the following: **1.1.1** Addition of a sieving step(s) for aggregate removal if it occurs under nonaseptic conditions.	The SUPAC guidance states that "process changes including changes such as mixing times and operating speeds within application/validation ranges" are Level 1 (annual report) changes; whereas "process changes including changes such as mixing times and operating

	1.1.2 Changes in mixing times for immediate-release solid oral dosage forms and for solution products. **1.1.3** Changes in drying times for immediate-release solid oral dosage forms."	speeds outside of application/validation ranges" are Level 2 (Changes Being Effected Supplement) changes. Please clarify whether the new guidance allows for changes to parameters listed above (mixing time, drying time) within or outside the validation range to be reported in the annual report.
3.3	"Replacement of equipment with that of the same design and operating principle that does not affect the process methodology or in-process control limits, with the exception of equipment used in aseptic processing (e.g., new filling line, new lyophilizer)."	This type of annual reportable equipment change without the exception for aseptic processing equipment is currently provided for in the Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004). By adding the qualifier "with the exception of equipment used in aseptic processing" some changes which used to be annual reportable (e.g., new freeze dryer) will now require a supplement. If the exception, as stated, is removed, changes to a new filling line would still fall under the requirements of the April 2004 Changes guidance and would not be annual reportable. In addition, this section as written is more restrictive than 314.70(d)(2)(iii). Furthermore, this item is in conflict with item 3.4, which would permit the addition of duplicate unit process for aseptic operations. Please revise item 3.3 as follows: "Replacement of equipment with that of the same design and operating principle that does not affect the process methodology or in-process control limits, unless otherwise provided for in applicable guidance (e.g., Guidance for Industry: Changes to an approved NDA or ANDA)." ~~with the exception of equipment used in aseptic processing (e.g., new filling line, new lyophilizer).~~

3.4	"Addition of a duplicate process chain or unit process in the drug substance and drug product manufacturing process with no change in in-process control limits or product specifications."	The meaning of "Addition of a duplicate …unit process" is not clear. It is not clear if this is intended to allow for repeat operations on a one-off basis and/or as routine processing. Please revise item 3.4 as follows: "Addition of a duplicate set of process equipment ~~process chain or unit process~~ in the drug substance or ~~and~~ drug product manufacturing process with no change in in-process control limits or product specifications."
3.5	"Addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of integrity test failures."	Addition of refiltration as an annual reportable change is restricted to filter integrity test failures. Other types of equipment failure (e.g., leaking tank valve) which may compromise sterility assurance should be eligible for refiltration. If the refiltration operation is performed in accordance with an approved protocol, the outcome of the refiltration is not dependent upon the event which prompted the refiltration. Please revise item 3.5 as follows: "Addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of integrity test failures or other equipment failures (e.g., leaking tank valve) which may compromise sterility."
3.7	"Changes to filtration process parameters (such as flow rate, pressure, time, or volume, but not filter materials or pore size) that are within currently validated parameters and therefore would not warrant new validation studies for the new parameters."	This example appears to allow the addition of a previously validated sterile filtration parameter to the NDA. The situations where this example would apply are rare. Reporting of changes within the validated range may not be necessary and may be burdensome. Please delete item 3.7 or revise it to be clearer.

3.9 (*Proposed)*	N/A	Please add a new bullet 3.9 to include any change within an approved design space in order to be consistent with ICH Q8R(2) guidance and concept of Quality-by-Design. "3.9 Any change within an approved design space consistent with ICHQ8R(2)."
3. Specifications		
4.1	"Addition of a specification for existing excipients."	Often the NDA describes excipients only as USP. In these cases, any changes in the USP monograph will be adopted by the manufacturer via internal change control systems. Please revise section 4.1 as follows: "4.1 An addition of a specification for existing non-compendial excipients." Additionally, please consider revising this statement to cover several types of changes to the specifications of existing excipients (e.g. addition, deletion, widening, tightening of tests).
4.2	"Change to a drug substance or drug product to comply with the official compendia can be reported in an annual report if it is: **4.2.1** A change to tighten an existing acceptance criterion; or **4.2.2** Other changes, except for changes to assays, impurities, product-related substances, or biological activities in approved NDAs and ANDAs."	Changes to drug substance or drug product assays, impurities, product-related substances, or biological activities require a supplement, even if the changes comply with the official compendia. Section 4.2.2 restricts reporting of changes to comply with official compendia beyond what is provided for in 314.70(c) and (d). 314.70(d)(2)(i) allows for annual reporting of any change to comply with a change to an official compendium except changes described in

		314.70(c)(2)(iii). 314.70(c)(2)(iii) provides for reporting the relaxation of acceptance criterion or deletion of a test to comply with an official compendium as a CBE-30. For example, a minor change to a USP test, e.g. specifying a reagent or clarifying text, would require a supplement under the text as written. Compendial revisions are reviewed through the compendial processes and determined not to adversely affect quality. FDA has an opportunity to review compendial changes and has an internal process to do so. Please revise section 4.2 as follows: "4.2 Change to a drug substance or drug product specification to comply with the official compendia except for relaxing an acceptance criterion or deleting a test. ~~can be reported in an annual report if it is~~ ~~**4.2.3** A change to tighten an existing acceptance criterion; or~~ ~~**4.2.4** Other changes, except for changes to assays, impurities, product-related substances, or biological activities in approved NDAs and ANDAs."~~
4.3	"Change in the approved analytical procedure if the revised method maintains basic test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims	Reporting minor changes to the analytical procedure such as changes to sample preparation or flow rate which do not impact the method analysis and are justified and documented need not be reported in an annual report. Reporting such changes may be overly prescriptive.

	to have or is represented to possess and the acceptance criteria remain unchanged (e.g., change in the flow rate or sample preparation for a high performance liquid chromatography (HPLC) method)."	
4.4	"Replacement of a nonspecific identity test with a discriminating identity test that includes a change in acceptance criteria (e.g., replacing *SDS-PAGE*11 with peptide map)."	Small peptides manufactured by chemical synthesis appear to be the intent of this example. However, given that biologic products to not appear to be included under the scope of this guidance, an alternative example that is more broadly applicable to a small molecule might prevent misinterpretation.
4.5	"Addition of an in-process test."	Companies may perform additional testing as an extra measure of quality control or for informational purposes. If the manufacturer proposes to remove an approved in-process test because it is redundant (e.g., an ID test is conducted at both crude and final API stage), and the change will have no impact on the quality of the drug substance, then this should be considered an annual reportable change. Please consider revising this item to read, "Addition of or replacement of an equivalent in-process test."
4.11	"Tightening of an existing acceptance criterion."	It is not clear why tightening of an acceptance criteria approved under the NDA should be reported. Companies may incorporate tighter acceptance criteria for internal quality purposes (e.g. external supplier agreements).
4.12 *(proposed)*	N/A	Consider including the deletion of alternate methods as an annual reportable change.

4.13 *(proposed)*	N/A	Please also consider making a change from an in-house method to a compendial method for excipients, API, and drug product as an annual reportable change.
5 Container/Closure System		
5.2	"Use of a contract manufacturing organization (CMO) for the washing of a drug product stopper, provided the applicant certifies that the CMO's washing process has been validated and the CMO's site has been audited by the applicant (or by another party Sponsored by the applicant) and found CGMP compliant."	This section allows for reporting the use of a CMO for washing drug product stoppers in an annual report. Since the stopper washing process may also include a stopper siliconization step, it should be clarified that this operation may also be included in the annual report notification. Please revise item 5.2 as follows: "Use of a contract manufacturing organization (CMO) for the washing or washing and siliconization of a drug product stopper, provided the applicant certifies that the CMO's washing and siliconization processes have been validated and the CMO's site has been audited by the applicant (or by another party Sponsored by the applicant) and found CGMP compliant."
5.3	"For solid oral dosage forms: **5.3.1** Elimination of bottle dunnage. **5.3.2** Change in type of desiccant to another equivalent desiccant that was previously used in another approved product."	Please clarify FDA's definition and interpretation of the term "bottle dunnage."
5.5	"Changes to a crimp cap (ferrule and cap/overseal), provided that there are no changes to the labeling or the	Please consider revising this portion of the guidance to also allow certain changes to the labeling on ferrules or

	color and that container and closure integrity have been demonstrated using a validated test method.”	caps. For example, if a company were to remove the words "Flip Off" or a company logo from a product cap, the resulting impact to the drug product would have a minimal potential to have an adverse impact on its identity, purity, strength, quality, etc., thus one would expect this change to be annual reportable. This example is particularly relevant because USP appears to be moving forward on restricting the kinds of wording and logos that can appear on injectable product caps and overseals. We also recommend that a change to the color of the overseal be annual reportable. (Also note: consider combining items 5.4 and 5.5 as "Change to primary or secondary packaging for parenteral drugs")