Biotechnology Innovation Organization

October 10, 2017

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

Re: Docket No. FDA–2017–D–2802: Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports; Draft Guidance For Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on FDA's Draft Guidance for Industry "Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports" (Draft Guidance).

BIO is the world's largest trade association representing 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.

I. General Comments:

BIO appreciates the Agency's efforts towards a categorization of listed annual reportable changes for biologics based on the associated commensurate risk, along with the annual reportable manufacturing type examples provided in the Draft Guidance. However, as recognized in the Draft Guidance, "BLA holders may, based on their specific circumstances, determine that a change described in the Appendix would appropriately be submitted as a supplement rather than in an annual report." As such, to minimize ambiguity in the future among applicants, we would recommend that the Final Guidance include examples of situations where annual reportable listed changes in the Guidance may be better categorized by applicants as a supplement based on certain specific circumstances. This could be in the form of an Annex to the Final Guidance, as a means of underpinning the principles to be considered by applicants in determining the applicable categorization to be used under certain circumstances, along with a better understanding of the Agency's current thinking on the topic.

Relatedly, it would also be helpful for FDA to acknowledge and confirm that a Sponsor can perform an impact assessment to determine if the proposed change may be reported in an annual report, even if the proposed change is not listed within the guidance. In other words, it would be helpful to provide clarity that the list in the appendix is not all inclusive.

Additionally, it would be helpful for FDA to define when the potential for an adverse effect is determined. Is it the potential at the first thought of the change, after a risk assessment, after generating some data, after validation, or at time of implementation? This is important

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because as the change is analyzed and data are generated generally the potential for adversely affecting the product decreases.

Finally, it will be important that this Guidance is aligned with the final ICH Q12 guideline once complete. To this end, BIO notes that continuity and consistency of terms across various guidances and guidelines will be necessary to ensure clarity and consistency in expectations for both Sponsors and Regulatory Authorities.

II. Examples/Situations from Other FDA Guidances:

There are a number of other FDA Guidances that discuss changes to an approved application related to CMC that are either reportable in the annual report and should be reflected in this guidance or that this Draft Guidance should be harmonized with to ensure consistent reporting.

2014 Guidance "CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports[1]"

Some of the annual reportable situations listed in this document may also be applicable for biological products. Some parallel examples from the 2014 Guidance to the Draft Guidance include:

- Section 3.5. – "For sterile drug products, addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of filter integrity test failures."

- Section 3.7. – "For sterile drug products, changes to the ranges of filtration process parameters (such as flow rate, pressure, time, or volume, but not pore size) that are within currently validated parameters ranges and therefore would not warrant new validation studies for the new ranges."

- Section 5.6. – "Change to delete the company trademark or other markings on the crimp cap (ferrule and flip cap/overseal) to comply with the official compendium."

- Section 7.3. – "For changes in an application that are fully consistent in scope and requirements with changes previously approved in a grouped supplement (also defined as a Bundled Supplement), the same applicant can make the same change to similar drug products."

Further, this same Guidance includes "For equipment used in aseptic manufacturing processes (e.g., new filling line, new lyophilizer), replacement of equipment with that of the same design and operating principle, when there is no change in the approved process methodology or in-process control limits." as a change that can be documented in annual reports. However in the Draft Guidance, line 234 excludes a new filing line or lyophilizer from the example to be reported in an annual report. We believe that the two guidances should be in agreement and that the Draft Guidance should allow a new filling line or

[1] FDA, "CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports" (March 2014)

lyophilizer to be included in an annual report provided there are no changes in the approved process methodology or in-process control limits.

1997 Guidance "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products[2]"

This Guidance includes "Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to an SOP on file in the approved license application" which should also be included in this guidance when finalized.

Additionally, this Guidance includes two annual reportable changes that are not included in this Draft Guidance. We ask FDA to clarify whether these should now be considered an unreportable change. These include:

- 4. "Replacement of an in-house reference standard or reference panel (or panel member) according to SOPs and specifications in an approved application"
- 10. "A change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications)"

1997 Guidance "Changes to an Approved Application: Biological Products[3]"

This Guidance includes relocation of equipment within approved operating room as an annual report. This represents minor risk to product quality for specified biological products and therefore should be listed in the new guidance.

III. Conclusion:

BIO appreciates this opportunity to comment on the Draft Guidance for Industry "Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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[2] FDA, "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products", (July 1997)
[3] FDA, "Changes to an Approved Application: Biological Products" (July 1997)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
III. RECOMMENDATIONS FOR REPORTING CERTAIN CHANGES IN AN ANNUAL REPORT		
Lines 104-105:	It would be helpful for FDA to clarify when the applicant would be notified of the correct category and the request for additional clarification. The uncertainty in timing of the Agency's response may hinder the Sponsor's ability to appropriately plan for the proposed changes aimed at mitigating risks.	BIO asks the FDA consider the following edits to the proposed guidance: "If FDA disagrees with the categorization, FDA may notify the applicant of the correct category and request additional information within 30 days of FDA receipt of a supplement."
Lines 132-135:	The Draft Guidance states, "For specific questions associated with whether the change should be submitted to the Agency in a supplement or documented in an annual report, we recommend that applicants contact the Office of Pharmaceutical Quality in CDER or the Office of Communication, Outreach and Development in CBER."	BIO asks FDA to provide further clarity on this process e.g., how should the request be provided, examples of information needed for the Agency to make a categorical determination, how is the request and Agency categorical determination of the proposed change at the time documented by the FDA, as well as communicated to the applicant, and what is the timing for receiving Agency feedback on their categorical determination of the proposed change.
IV. CONTENTS OF AN ANNUAL REPORT NOTIFICATION		
Line 154:	The Draft Guidance discusses "a list of all products involved."	BIO asks FDA to clarify what is meant by "list of products." BIO interprets this to mean different presentations and/or strengths of the same active ingredient registered under the same application. Additionally, we ask FDA to clarify the level of information being requested for "a list of all products involved." Is the FDA requesting a list of other commercial products, including BLA number?

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Lines 160-161:	The Draft Guidance states, "If the submitted change is inappropriate for documentation in an annual report, FDA may notify the applicant of the correct category and may request additional information." Annual reportable changes are reported after implementation and product manufactured with the change would potentially be in the market. Therefore, it is important that FDA provides guidance on the impact to distributed product in situations in which FDA disagrees with the company assessment of "minimal potential to have an adverse impact on product quality." Furthermore, the Agency should facilitate a Sponsor's ability to plan appropriately to minimize any potential risks by setting out a clear timeframe by which Sponsors should expect Agency's response.	BIO asks that FDA include when (timing) an applicant would receive such a notification. We suggest this notification be within 30 days. As such, we suggest editing the text to read: "...may request additional information. FDA will provide recommendation to the company with respect to the impacted product that is already distributed or is ready to be distributed, within 30 days of receipt of a supplement."
APPENDIX: EXAMPLES OF CMC POSTAPPROVAL MANUFACTURING CHANGES THAT FDA GENERALLY CONSIDERS TO HAVE MINIMAL POTENTIAL TO HAVE AN ADVERSE EFFECT ON PRODUCT QUALITY		
Lines 172-174:	The Draft Guidance states, "Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses. Note that this does not apply to loss of potency during storage." BIO notes that ICH Q8, Section 2.2.2 states that overages are included to compensate for manufacturing losses, not degradation. An overage would be directly related to nominal label claim.	BIO asks FDA to discuss if there are instances that elimination or reduction of an overage would be an annual reportable change. An example would be helpful to illustrate this point.

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Line 176:	Deletion of manufacturing sites has no risk to product quality and therefore a notification should be provided to communicate the change to avoid continuous inspections.	BIO suggests adding the following text to this section: "Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)."
Lines 178-185:	The Draft Guidance discusses the site change for testing example. BIO believes that as long as the new site has already demonstrated ability to perform similar testing (e.g., potency/bioassay, sterility, or virus testing), and is CGMP compliant, this type of change can be managed under GMP Quality systems with minimal risk. BIO also notes that normally, analytical methods are transferred between laboratories using pre-defined protocols and/or established procedures designed to show equivalence between the resting and receiving labs.	BIO suggests editing the text to read: "Site change for testing, ~~This includes sites for testing of lower risk process-related impurities (e.g., host cell proteins, host cell DNA, residual solvents)~~ when the method has been ~~was~~ successfully validated ~~at the new site~~ and or transferred to the new site, where applicable, meets relevant cGMP requirements for the type of testing ~~operation~~ involved (e.g., no outstanding FDA warning letters or "official action indicated" compliance status). ~~This does not include sites for testing for conformance to quality control specifications, including potency, impurities (except those that are lower risk), and safety testing (e.g., sterility and virus testing).~~" BIO believes it would also be helpful for the guidance to address whether the term "validated" includes test method site transfers or test-site verification of the respective test
Lines 182-185:	The Draft Guidance states, "This does not include sites for testing for conformance to quality control	Further clarity around 'conformance to quality control specifications' would be helpful and avoid confusion.

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	specifications, including potency, impurities (except those that are lower risk), and safety testing (e.g., sterility and virus testing)." BIO notes that this text seems to contradict itself. The way this is currently worded would exclude site change for testing as annual reportable with the exception of low risk impurities. Should compendial assays such as pH, osmolality, etc. also be considered low risk? Viral testing seems to be a lower-risk test (MWCB and harvest) as the safety testing of the cell banks and harvest samples from the approved process is provided in the initial BLA.	As such, BIO suggests FDA use "conformance to specifications" as in ICHQ6A. As such, BIO suggests revising the text to read: "This ~~does not~~ includes sites for testing for conformance to ~~quality control~~ specifications *except for* ~~including~~ potency, impurities (except those that are lower risk), and safety testing (e.g., sterility ~~and virus testing~~)."
Lines 187-188:	The Draft Guidance states, "Site change for labeling or secondary packaging when the new site has a satisfactory CGMP status." BIO notes that in the Guidance for Industry- Changes to an Approved NDA or ANDA Questions and Answers (Manufacturing Sites, A4) FDA states, "The site should have a satisfactory inspection relating to packaging operations for notification to occur in the annual report. For the purposes of this guidance, in general, there is no two-year limit on the CGMP inspection."	BIO suggests that FDA revise this language to be consistent with previous FDA guidance that there is not a 2-year limit on the cGMP inspection. As such, BIO suggests editing the text to read: "Site change for labeling or secondary packaging when the new site has a satisfactory CGMP status for these operations. There is not a 2-year limit on the cGMP inspection."
Lines 190-194:	The Draft Guidance discusses the example regarding change in the location of manufacturing steps within a manufacturing area.	BIO suggests editing the text to read: "Change in the location of manufacturing steps within a manufacturing ~~area~~ facility that is already listed in

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	BIO believes that the designation of manufacturing area is vague. Area could be construed to mean only within the same suite, within the same building or on the same site. Additionally, changes in location of non-sterile portions of drug product manufacturing such as formulation steps should also be annual reportable.	an approved BLA where those steps are part of a nonsterile drug substance production process or nonsterile steps of drug product manufacturing (e.g., formulation) and the new location will have no impact or will lower the risk of contamination or cross-contamination (e.g., improved air classification, better process flow, enhanced segregation of pre- and post-viral inactivation steps)."
Lines 196-198:	BIO believes it would be helpful to include a few examples of low risk modifications to a manufacturing facility. Some of these changes (HVAC) were included as annually reportable in the Guidance for Industry on Changes to an Approved Application: Biological Products from July 1997. Additionally, we believe that changes to or refurbishment of a sterile manufacturing area may be reported in the AR if the data submitted support no change in sterility assurance.	BIO suggests editing the text to read: "Modification of a manufacturing facility listed in an approved BLA that is appropriately qualified per GMP requirements and does not increase the risk of contamination (e.g., affect sterility assurance) or if the data submitted support no change in sterility assurance or otherwise present a meaningful risk of affecting product quality (e.g. minor changes to floor plans and flows with direct product impact, new or modified HVAC. Modifications of a manufacturing facility (e.g. minor changes to floor plans and flows) that have no direct product impact are not reportable. These changes will be documented in the Site Master File floor plan and flow diagrams."
Lines 200-202:	The Draft Guidance discusses the manufacture of an additional drug product. BIO notes that the introduction of both Drug Substance and Drug Product in a multiple-product area is low risk to product quality under the specified conditions (2.5.1, 2.5.2 and 2.5.3).	To avoid ambiguity in interpretation, please edit text to include introduction of Drug Substance and Drug Product: "~~Manufacture of an additional~~ Introduction of a new drug product ~~and~~ or drug substance (already licensed or an investigational product), in a multiple-product

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		area listed in an approved BLA that is producing other products, if:"
Lines 204-205:	The Draft Guidance discusses specific identity tests. BIO notes that during introduction of new product, the main concern is regarding possible errors and cross contamination in the multiple-product area. Therefore, it will be important to have an appropriate control strategy in place.	BIO suggests editing the text to read: "~~Specific identity tests exist to differentiate~~ Appropriate control systems to prevent error and cross-contamination between all products manufactured in multiproduct area ~~at the facility;~~ and"
Line 218:	This section of the Draft Guidance discusses examples regarding manufacturing process, batch size, and equipment.	BIO believes that the annual reportable change categories for "Manufacturing Process, Batch Size, and Equipment" should include a category regarding "no change" in conditions e.g., "like to like" equipment changes.
Line 218:	The improvements associated with automation or inspection equipment represent minor risk to product quality and therefore should be listed in the new guidance.	BIO suggests adding the following text to this section: "Automation of one or more process steps without a change in process methodology as well as improvements of inspection equipment and /or system for detection of defects."
Line 220:	The Draft Guidance discusses changes in mixing times for solution dosing forms. BIO believes that changes to mixing parameters for buffers and solutions, or for freeze dried product, along with solution dosage forms, have minimal risk to product quality and as such should be included in	BIO suggests editing the text to read: "Changes in mixing ~~times~~ parameters for buffers, medias, and solution dosage forms or freeze-dried products."

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	the annual report. Characterization/ qualification data supports the new mixing parameters. Additionally, the mixing of buffers, medias and solution dosage forms includes both a mixing time and speed; therefore, we propose replacing "times" with "parameters" because it is a more representative and comprehensive term.	
Lines 222-224:	BIO believes that to bring clarity to context, it will be helpful to add description. Additionally, "small changes" is vague and subjective. Would the requirement to meet all in-process control limits be sufficient since subsequent lines (226-228) requiring that the change not involve different equipment would limit scope. Please delete the word or provide clarification.	BIO suggests editing the text to read: "Manufacturing batch size or scale change due to ~~small~~ changes in the size of pooled or separated batches to perform the next step in the manufacturing process if all batches meet the approved in-process control limits and the critical process parameter ranges for the next step remain unaffected."
Lines 226-228:	The Draft Guidance discusses changes to batch sizes that do not involve use of different equipment. Minor equipment differences are occasionally required for facility flexibility to implement the examples listed for change in batch size. Minor changes in chromatography column size, such as column diameter, are lower risk than minor increases in load volume, and do not result in impact to product quality and as such should be reportable via the annual report. Additionally, to clarify that the changes to batch size encompass both Drug Product and Drug Substance,	BIO suggests editing the text to read: "Changes to drug product and drug substance ~~batch sizes~~ that do not involve use of significantly different equipment (e.g., increase in roller bottle number, minor increases in fermentor volume, or minor increases in load volumes/column size for chromatography columns, or minor increases in number of filled units)." BIO also believes that the phrase "minor increases" is vague and subjective. As such, it would be helpful if FDA include more discussion regarding what

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	it will be helpful to include an example on DP (e.g. minor increase in number of filled units).	"minor" in these cases mean, perhaps by example or a condition to be fulfilled.
Line 229:	BIO views a change in column diameter to increase bed volume to be lower risk than going outside of the previous load range. The same is true for assessments on increasing filter area on a UDF filter. Bed height, column pressure drop, linear velocity and other characterized process parameters within existing operating ranges would be maintained.	As such, we suggest adding a new bullet: "3.X Changes to chromatography column diameter, column model, or column skid that maintain the same operational ranges (e.g., bed height, linear velocity, loading per liter of resin, temperature, and other relevant process parameters) and use the same column type and resin."
Lines 230-234:	The examples listed provide facilities flexibility to adjust production to ensure product availability with minimal potential to impact product quality. In the case of column diameter, the proposed increase is far less than the up to 100X difference in scale-down models used for critical safety parameters (e.g., viral clearance, resin re-use). Additionally, all critical process parameters are characterized in S.2.6, even though minimal changes to performance parameters are required. Additionally, per our comment in the general comments above, BIO believes that new filing lines and new lypophilzers should be allowed to be included in the annual report provided there is no change in the approved process methodology or in-process control limits. BIO also notes that the phrases "an identical duplicate process chain or unit process" and "…with no change to equipment…" are unclear.	BIO recommends editing the text to read: "Addition of an identical duplicate process chain or unit process in the drug substance and drug product manufacturing process on the same manufacturing site with no change to ~~equipment,~~ process methodology, in-process control limits, process parameter ranges, or product specifications, with the exception of addition of major equipment used in aseptic processing ~~(e.g., new filling line, new lyophilizer)~~. Minor drug substance equipment changes (e.g. larger pooling tank (same materials of construction), minor increase in column diameter (e.g. 60 to 80 CM with no change in linear flow rates, or other performance parameters), increased number UF/DF cassettes (identical membrane type, same relative flow rates)) when changes are either supported by characterization, or do not impact performance parameters listed in the marketing application."

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	Finally, It would be helpful for FDA to clarify if there are restrictions that such changes be within the same facility or just one the same manufacturing site.	Additionally, BIO suggests defining and clarifying the phrases "an identical duplicate process chain or unit process" and "…with no change to equipment…". It may also be helpful to include examples.
Line 230:		BIO asks FDA to clarify whether a new identical Production Bioreactor falls into scope in Section 3.4 that can be submitted as annual reportable change as long as it is an identical bioreactor and there is no process change.
Lines 245-246:	The Draft Guidance discusses sterilization chambers and validated parameters. BIO believes that if parameters change, and validation is completed successfully again, these changes should be able to be considered for annual reporting, as long as the validation sterilization parameters do not change. Suggest adding this important differentiation.	BIO suggests editing the text to read: "…operate within the previously validated sterilization parameters. This does not include situations that change the validat~~ion~~ed sterilization parameters."
Line 247:	The Draft Guidance provides feedback on the container closure, but does not provide any additional details regarding secondary packaging. It would benefit Sponsor if the guidance included the Agency's recommendations on secondary packaging in order to enhance consistency with and clarity on Agency expectations.	BIO suggests adding a section 3.7: 3.7. For drug product container outer surfaces sterilization, change from a qualified sterilization chamber (e.g. vaporized hydrogen peroxide) to another of the same design and operating principle for blister package/ drug product container preparation when the new chamber and load configurations are validated to operate within the previously validated parameters. This does not include situations that change the validation parameters.

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Line 250:	The Draft Guidance discusses the addition of tests and acceptance criteria for excipients. BIO believes that the addition of DS and DP testing and acceptance criteria that are minimal risk to be included in this statement.	BIO suggests editing the text to read: "Addition of tests and acceptance criteria to specification for approved excipients, drug substances, and drug products."
Lines 252-254:	The Draft Guidance states, "Change to a drug substance or drug product to comply with an official compendial test, except for changes to assays, impurities, product-related substances, or biological activities or changes described in 21 CFR 601.12(c)(2)(iv)." According to 21 CFR601.12, any change made to comply with a change to an official compendium is annual reportable, except for relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. The Draft Guidance increases the regulatory burden by excluding these changes from annual report: changes to assays, impurities, product related substances, or biological activities to comply with compendia.	BIO believes that a change to an "excipient with an official compendial test" should also be included, and that the Agency is referring to "tests for impurities." As such, BIO suggests editing the text to read: "Change to a drug substance or drug product to comply with an official compendial test, except for ~~changes to assays, impurities, product-related substances, or biological activities or~~ changes described in 21 CFR 601.12(c)(2)(iv)."
Line 256:	BIO notes that the term "regulatory analytical procedure" is not defined in this Draft Guidance but is a defined term in the reference Guidance for Industry Analytical Procedures and Methods Validation Chemistry, Manufacturing, and Controls Documentation.	For clarity, we propose that if the Agency is using this term it should either be defined in text or reference the guidance mentioned above. If this is not the Agency's intent or if the Agency is not in agreement with including the reference or definition, then we would suggest editing the text to read:

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		"Change in the ~~regulatory~~ approved analytical procedure if the product acceptance criteria remain unchanged and the revised method maintains basic test methodology (e.g., change in the flow rate or sample preparation for an HPLC method) 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 to have or is represented to possess."
Lines 263-265:	The Draft Guidance discussing replacing a nonspecific identity test.	BIO asks FDA to clarify whether the replacement method is for release or in-process testing or both.
Line 267:	The Draft Guidance discusses the addition of an in-process test. BIO believes it would be helpful to clarify if the submission category would change when the addition of an in-process test is resulted from a quality issue.	As such, BIO suggests revising the text to read: "Addition of an in-process test provided this is not the result of a quality issue."
Line 271:	The Draft Guidance discusses tightening of an existing acceptance criterion.	BIO suggests editing the text to read: "Tightening of an existing acceptance criterion for the drug substance, drug product, excipients or in-process materials."
Lines 275-279:	The Draft Guidance states: "Change in the container closure system for the storage of a nonsterile drug substance when the proposed container closure system has no increased risk of leachable substances (based on the extractables and/or leachables profile and whether stability data are consistent with	BIO notes that some biologic products are sensitive to light. As such, we suggest revising the text to read:

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	historical trends), and the new container offers equivalent or greater protection properties from air and moisture."	"…and the new container offers equivalent or greater protection properties from air and moisture, and light (for light sensitive products)."
Line 281:	The Draft Guidance discusses use of a contract manufacturing organization for the washing of a drug product.	BIO suggests that along with the use of a CMO for component washing, that change in or addition of a CMO for component washing be in scope of annual reporting.
Lines 286-288:	The Draft Guidance states: "Changes to a crimp cap (ferrule and cap/overseal), provided that there are no changes to the labeling or the color and that container closure integrity has been demonstrated using a validated test method."	BIO suggests adding additional clarification that the commercial line should be used for capping for the demonstration of CCIT. As such, we suggest editing the text to read: "Changes to a crimp cap (ferrule and cap/overseal), provided that there are no changes to the labeling or the color and that container closure integrity has been demonstrated for vials capped using the commercial equipment and using a validated test method."
	BIO asks FDA to consider adding the following section and examples.	"6. Analytical and Stability 6.1. Implementation of a new reference standard when new reference standard is established and qualified per approved protocol. 6.2 Implementation of a drug substance or drug product shelf-life extension in accordance with 3.2.S.7.2 or 3.2.P.8.2, or other approved protocol."