March 22, 2018

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

Re: Docket No. FDA-1995-D-0288: Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products; Draft Guidance for Industry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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on FDA's Draft Guidance for Industry "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products" (Draft Guidance).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.

BIO appreciates that the FDA is updating this Guidance to "accommodate advances in manufacturing and testing technology and to clarify FDA's current thinking on assessing reportable changes" (page 2). BIO is supportive of the FDA's efforts to update and replace the 1997 version of this Guidance. BIO believes that the current Guidance is outdated and leads to unnecessary misunderstandings of what constitutes a regulatory change and the resultant change category. As such, we believe that this update provides further guidance on assessing and reporting CMC changes to the biological products within the document's scope and are pleased that FDA is reviewing and updating guidances as appropriate.

To that end, we also recommend that the FDA revise the Agency's Guidance on "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products," which is also dated July 1997, so that a risk-based approach, along with a listing of more current examples of post-approval manufacturing changes and recommended reporting categories is reflected in both guidance documents. This would promote consistency and lessen ambiguity with regards to evaluating and reporting CMC changes for biologics in general.

BIO appreciates that cellular, gene, and cell-based gene therapy products are included in the scope of the Draft Guidance. However, we note that some of these products are excluded as exceptions in certain examples in the provided Appendix. To promote longevity of this Guidance, when finalized, as more of these products are approved, we recommend a risk-based approach be adopted based on the level of evidence needed for the categorization of post-approval changes for these products. Secondly, some examples specify or exclude "cellular and cell-based gene therapy products" (page 20 and 40), others

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use the terms "cellular therapy and cell-based gene therapy products" (page 20), "gene therapy" products (page 23) or "cellular and gene therapy products" (page 26 and 27). In the Final Guidance, BIO suggests FDA clearly define and distinguish these products types using consistent terminology with examples where possible and appropriate.

Additionally, BIO suggests that additional risk-based decision-making be incorporated into the change categorization to aid Sponsors. Finally, it will be important that this Guidance is aligned with the final ICH Q12 guideline once complete and other final ICH guidelines. 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.

Conclusion:

BIO appreciates this opportunity to comment on the Draft Guidance for Industry "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products." 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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/S/

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
III. SCOPE		
Page 3:	The text discusses which biological products are in and out of scope of the Draft Guidance. While the Draft Guidance mentions vaccines generally, it is unclear whether therapeutic vaccines are considered in or out of scope.	BIO suggests that if therapeutic vaccines are in scope of the Guidance that a bullet be added, specifically listing them.
IV. REPORTING CHANGES		
A. *Reporting Categories*		
B. *Assessing and Implementing Manufacturing Changes*		
Page 6, bullet 2:	The Draft Guidance includes "Development and manufacturing of the drug substance" as a consideration to take into account when assessing the impact of a change on product quality. Historical knowledge of development and manufacturing of the drug substance, as well as the drug product, should be taken into account when assessing change.	BIO suggests editing the text to read: "Development and manufacturing of the drug substance and drug product.
Page 7, paragraph 2:	The Draft Guidance states "Conducting and submitting to the FDA formal or informal risk assessments in support of a post-approval manufacturing change can allow the FDA to conduct a more effective assessment of the impact of a change, thereby facilitating timely review and decision."	BIO suggests editing the text to read: "Conducting and submitting to the FDA formal or informal risk assessments in support of a post-approval manufacturing change can allow the FDA to conduct a more effective assessment of the impact of a change, thereby facilitating timely review and

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	However, the Draft Guidance does not discuss in which CTD section the risk assessment should be located.	decision. The risk assessment should be provided in 3.2.R."
Page 7, paragraph 2:	The Draft Guidance states "Conducting and submitting to the FDA formal or informal risk assessment in support of a post-approval manufacturing change can allow the FDA to conduct a more effective assessment of the impact of a change, thereby facilitating timely review and decision." However, BIO believes that it unclear what is meant by "formal or information risk assessment".	BIO asks FDA to discuss in more detail what is considered an informal and a formal risk assessment and their respective uses. Specifically, BIO seeks additional detail around timelines of these FDA assessments and whether all quality risk assessments (QRAs) must be submitted prior to any work beginning.
C. *Submission of Changes to FDA*		
Page 8, paragraph 3, bullet 5:	The Draft Guidance includes "Relevant validation products and data" as an item to include in any supplement. BIO believes that the submission of a validation protocol should not be required if applicable data and/or reports are provided.	BIO suggests editing the text to read: "Relevant validation ~~products and~~ data" Additionally, we ask FDA to provide clarity on whether all validation protocols and reports are required in all supplements and whether these must be provided (translated) in English.
Page 8, paragraph 3, bullet 6:	The Draft Guidance includes a "reference list of standard operating procedures (SOPs)" as an item to include in any supplement. BIO does not believe that a reference list of SOPs should be required to assess the impact of the	BIO suggests deleting this from the list of information included: "~~reference list of standard operating procedures (SOPs)~~"

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	change on product quality. SOPs are reviewed as part of GMP inspections.	Alternatively, we ask FDA to allow the relevant SOPs to be referenced within the Sponsor's internal documentation rather than providing the entire list in the Annual Report (AR).
Page 8, paragraph 4, first bullet:	The Draft Guidance includes "A list of all products involved in the change" in the items to include in an AR. BIO believes that this can be interpreted to mean different presentations and/or strengths of the same active ingredient registered under the same application or a list of other commercial products not covered under the BLA to which the AR is being submitted. The latter seems unnecessary since the focus of the AR is to capture and review changes specific to that BLA.	BIO asks FDA to clarify what it means by "all products".
Page 8, paragraph 4, sub-bullet 4:	The Draft Guidance discusses "relevant data from studies and tests performed to evaluate the effects of the change on product quality".	BIO asks FDA to clarify if reference to the data may be made instead of providing the data in an AR (this would not include stability data). Alternatively, FDA could allow applicants to include relevant references to studies performed to evaluate the effects of the change on product quality in the AR.
Page 9, bullet 1:	The Draft Guidance includes "A statement by the holder of the approved application or license that the effects of the change have been assessed" in the list of things to include in an AR.	BIO suggests deleting this bullet: "~~A statement by the holder of the approved application or license that the effects of the change have been assessed~~"

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	BIO believes that this should not be required within the submission of a change. Additionally, this item does not add value. Assessment of a change is inherently part of the change control process and is already included in quality systems. By the time a submission is made to support a change, it is inherent that the change has been assessed.	
D. *Comparability Protocols*		
Page 9:	BIO suggests harmonization of language via the use of the term "Postapproval Change Management Protocol" instead of comparability protocol.	BIO suggests replacing "comparability protocol" with either Postapproval Change Management Protocol (PACMP) or adding PACMP in addition to "comparability protocol" for clarity and harmonization of terminology.
Page 9:	The Draft Guidance discusses comparability protocols (CPs). While BIO believes that CPs for major manufacturing changes is clear, we find that information regarding "approved protocols" that are used to downgrade a change to an annual reportable change (e.g., reprocessing protocols) unclear.	BIO believes additional discussion and clarity of what changes may be provided as a protocol upfront for the purposes of having them reportable via an AR would be helpful.
Page 9:	BIO notes that that not all updates for CPs require a Prior Approval Supplement (PAS). For example, a moderate change to acceptance criteria that would be considered CBE30 for a process can also be submitted as CBE30 to update the CP.	BIO suggests editing the text to read: "A CP, ~~or a change to a CP,~~ shall be submitted as a PAS (a major change) requiring approval from the FDA before distribution of a product made using the change outlined in the protocol. A change to an approved CP shall be submitted as a PAS (major change) or CBE30 (moderate change) in accordance with examples in the Appendix."

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Page 9, paragraph 2:	The Draft Guidance indicates that a CP may be submitted for a single or multiple related changes, and may cover a single or multiple BLAs.	BIO asks FDA to clarify whether a CP can be applied across multiple sites under the same license.
E. *Recommendations for Reporting Categories*		
Page 9, last paragraph:	The Draft Guidance discusses selection of a reporting category. Sponsors should be able to assess changes and select a reporting category without having to discuss with FDA in advance. Additionally, it is already part of the review process for FDA to let the Sponsor know if they deem the reporting category differently.	BIO suggests editing the text to read: "Although the selection of a reporting category for a change should be made in accordance with existing regulations and the recommendations provided in this guidance, a different selection may in some instances be deemed appropriate ~~following discussion with the FDA~~."
F. *Implementing Changes to Approved Established Conditions*		
Page 10:	As written it is unclear whether established condition (EC) changes must be PAS, but changes that are not EC do not require reporting. Also, it is unclear how ECs are managed and presented in a dossier application.	BIO asks FDA to clarify their intention regarding EC changes and changes not in the EC being annually reportable or controlled by a pharmaceutical quality system (PQS) and thus not reportable.
Page 10:	While the Draft Guidance discusses implementing changes to approved established conditions, BIO notes that established conditions are not defined for legacy products via registered details (pre-eCTD).	BIO suggests adding the following text to this section: "For products approved prior to the eCTD format, consult with the appropriate FDA Review Division."
V. SPECIAL CONSIDERATIONS		
A. *Change in Process Parameters*		
Page 11, section A:	BIO finds the language regarding process parameters to be confusing.	BIO suggests that this section be aligned with ICH, specifically ICH Q8.

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		Additionally, we suggest editing the text to read: "~~Any~~ Changes ~~to process parameters (operating or performance)~~ in process parameters linked to product quality outside of an approved validated range(s) should be evaluated with respect to criticality, impact on process performance and product quality, and effectiveness of the overall control strategy and must be reported to the FDA."
B. *Change in a Supplier of Raw Materials*		
Page 11, section B:	The Draft Guidance discusses changes in a supplier of raw materials to be reported as a CBE30.	BIO believes that further differentiating a change of a supplier while still meeting the approved quality standard versus a change to the quality standard would be helpful.
Page 11, section B:	The Draft Guidance discusses changes in a supplier of raw materials reported as a CBE30.	BIO asks FDA to specify if animal derived versus non-animal derived impacts the filing category.
Page 12, first paragraph:	The Draft Guidance discusses changes to be reported in an AR or controlled under a quality system. BIO finds this language confusing. It is unclear whether the listed changes are reportable (in an AR) or not (controlled under a firm's pharmaceutical/device quality system). If the intent is that industry reports changes to key items but does not report changes to "others", then the Draft Guidance should include more detail and clarification.	BIO suggests editing the text to read: We recommend the following manufacturing change be reported in an AR ~~or be controlled under a firm's pharmaceutical/device quality system, as appropriate~~: Or if the intent is to have the changes either in an AR or in a quality system, we ask the FDA to include more clarification and detail around this difference. Additionally, BIO recommends specifying manufacturer of the material instead of the supplier:

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		"A change in a ~~supplier~~ manufacturer of key raw materials, reagents, and solvents that have a minimal potential to affect product quality, provided that the materials' specific use, physicochemical properties, impurity content, and acceptance criteria remain unchanged."
VI. GLOSSARY		
Page 12, Container Closure System (CCS):	The container closure system always includes secondary packaging. The primary container closure system does not, but the generic term "container closure system" does include secondary packaging. Additionally, drug substance and/or intermediates are discussed later in the Appendix, it would be useful to include those items here as well.	BIO suggests editing the text to read: "The sum of packaging components that together contain and protect the dosage form (Drug Substance, critical intermediates, and Drug Product). The CCS includes primary packaging components; it can also include secondary packaging components~~, if these are intended to provide additional protection to the Drug Product~~."
Page 13, Control Strategy:	BIO finds the definition of control strategy with regard to changes to alert/action limits unclear; limits to production intermediates are mentioned as a CBE on page 40.	BIO asks FDA to clarify whether changes to alert/action limits are considered to be part of the control strategy. If so, please include in the definition.
Page 13:	BIO believes that a definition for the term "intermediate" would be helpful.	BIO suggests adding the term "intermediate" into the glossary with the definition from ICH Q5C: "Intermediate: For biotechnological/biological products, a material produced during a manufacturing process which is not the drug substance or the drug product but whose manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications

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		will be established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes material which may undergo further molecular modification or be held for an extended period of time prior to further processing."
Page 14, Process Parameters:	Any change to PPs (operating or performance) outside of an approved validated range(s) has to be reported as PAS. BIO notes that the definition of PP is not aligned with ICH Q8 and some changes with no quality impact has to not be reported as PAS.	BIO suggests linking a change of a PP to the quality impact based on risk assessment. Depending of the risk, the level of submission should be aligned (i.e., potential major impact as PAS, medium as CBE30, low as AR and no impact as internal change without taking into account if the information is located in the BLA).
Page 14, Master Virus Seed:	BIO believes that viruses used in products that are not vaccines should be included in the definition of "master virus seed".	BIO suggests editing the text to read: "**Master Virus Seed** - A viral seed of a selected ~~vaccine~~ virus from which all future ~~vaccine~~ production will be derived, either directly or via Working Virus Seeds. (Ref. 17)"
Page 15, Reprocessing and reworking:	The difference and limits between reprocessing and reworking are not very clear.	BIO asks FDA to add more clarity on the definitions of reprocessing and reworking with examples. This is also applicable for P.3.3 (page 30). BIO also suggests adding a sentence to clarify whether a submission or notification is required for reprocessing. In the Appendix (page 22 and page 30) reprocessing is listed as a PAS without an approved protocol.

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Page 15:	BIO suggests adding a definition for "unit operations" since there are possible scenarios where divergent opinions may be reached; for example, manufacturing process steps consisting of various steps of purification comprising of a number of chromatography steps.	BIO suggests adding a definition for "unit operations".
VII. REFERENCES		
APPENDIX		
Page 19, row 5, column 1:	As written "change in unit operations" is vague and implies all changes are a PAS, which is contradictory to other changes identified in this Draft Guidance. As such BIO suggests writing as a more affirmative, clear statement.	BIO suggests editing the text to read: "Change in ~~unit operations and their~~ the sequence of unit operations, ~~including~~ addition, deletion, or substitution of unit operation(s)." We also suggest including the definition of "unit operations" in the glossary.
Page 19, row 6, column 2:	BIO suggests an additional item under "Changes to the Upstream Steps of Drug Substance Manufacture through Harvesting."	BIO suggests adding the following as a CBE30: "A change with moderate potential to adversely impact quality of the product (e.g., extension of the in vitro cell age beyond validated parameters)."
Page 19, row 6, column 2:	BIO suggests an additional item under "Changes to the Upstream Steps of Drug Substance Manufacture through Harvesting."	BIO suggests adding the following as a CBE30: "No change in the proportionality of the raw materials (i.e., the scale-up is linear). The scale-up involves the use of the same bioreactor (i.e., does not involve the use of a larger bioreactor)."

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Page 19, row 7, column 1:	Change in growth conditions and/or media composition is listed as PAS, however depending on the stage of the process (such as during cell culture scale up steps) no product may be being produced, thus there is minimal to no impact to product at this point. Changes to growth culture conditions at steps in the process where no product is being produced should be able to be submitted as a CBE30.	BIO suggests editing the text in column 1 (PAS) to read: "Change in the growth culture conditions at the production step (e.g., time, temperature, pH, etc.) and/or media composition outside of the parameters specified in the approved BLA." And adding text in column 2 (CBE30) that reads: "Change in the growth culture conditions in processing steps where no product is produced (e.g., time, temperature, pH, etc.) and/or media composition outside of the parameters specified in the approved BLA."
Page 20, row 2, column 1:	The text "change in batch size" is vague and unclear. BIO believes the Draft guidance needs to be clear on what constitutes a significant change in batch size.	BIO asks FDA to provide clarity as to what constitutes a change in batch size (e.g., change in fermenter size, increase in yield).
Page 21, row 3, column 2:	BIO suggests adding an additional item under "Change in the Drug Substance Purification Process."	BIO suggests adding the following to column 2 (CBE30): "A change to the control strategy to improve the probability of the process delivering the desired CQAs more consistently."
Page 21, row 3, column 2:	BIO suggests adding an additional item under "Change in the Drug Substance Purification Process."	BIO suggests adding the following to column 2 (CBE30): "Change in the parameters of an approved holding step or addition of a new holding step."

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Page 21, row 3, column 3:	BIO suggests adding an additional item under "Change in the Drug Substance Purification Process."	BIO suggests adding the following to column 3 (AR): "Addition of an in-process control (IPC). Tightening of acceptance criteria."
Page 21, row 4, column 2:	BIO notes that duplication of a like for like process train should be reported as an AR as a like for like change would have minimal potential to impact the product. If there are minor changes to the equipment that would increase the risk, then these types of changes should be reported as CBE30.	BIO suggests moving this change from column 2 (CBE30) to column 3 (AR).
Page 21, row 5, column 1:	The Draft Guidance categorizes an "Increase in the number of cycles of resin and membrane re-use without an approved protocol" as a PAS.	BIO proposes that the increase in the number of resin cycles be a CBE30 rather than PAS with conditions around impurity profile, carry over and physical characteristics. [Reference: Draft ChromPAC Guidance; PDA TR #38] As such, BIO suggests moving this from column 1 (PAS) to column 2 (CBE30) and editing the text to read: "Increase in the number of cycles of resin and membrane re-use without an approved protocol, based on data collected (full scale and/or small scale) provided there is no change in impurity profile, carry-over, and physical characteristics (e.g., back pressure)."

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Page 21, row 5, column 2:	A change in the "resin supplier with no change in the resin material, operating or performance parameters" is currently classified as CB30 change. However, a like-for-like replacement with a new supplier does not change the material attributes and as such this change could be handled via an AR since this is a low impact change.	BIO suggests moving the text in column 2 (CBE30) to column 3 (AR).
Page 21, row 8, column 1:	The Draft Guidance includes new or revised purification process as a PAS change.	BIO believes it would be helpful to include conditions related to "revised purification processes". For example, the listed PAS classification may be better suited as a CBE30 or Annual Report based on the revision made (i.e., major or minor, depending on the impact to product quality). Also, for clarity, BIO asks FDA to specify that the above PAS classification applies only in case if the revision is outside the validated range and not a revision of target (especially in case of elution rate).
Page 22, row 5:	BIO notes that readers of the Draft Guidance may go straight to the Appendix thus missing the items listed in the Special Considerations.	BIO suggests including the changes from Section V.B to this section of the Appendix.
Page 23, row 3, column 2:	BIO suggests adding an additional item under "Changes to the cell banks/cell seeds."	BIO suggests adding the following in column 2 (CBE30): "Change in cell bank/seed bank manufacturing site." Additionally, BIO believes a discussion regarding the appropriate category for adding an approved

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		manufacturing site to a different BLA would be helpful.
Page 23, row 3, column 3:	BIO suggests adding an additional item under "Changes to the cell banks/cell seeds."	BIO suggests adding the following in column 3 (AR): "Extension of the shelf life of cell banks or cell seeds used in the manufacture of cellular therapy, viral and bacterial vaccine products provided the change is made based on a protocol approved in the application."
Page 23, row 4, column 3:	A note stating "this does not apply to gene therapy products" is included. However, there is no context provided as to what the appropriate change category would be for cell/gene therapy products.	BIO suggests that the reportability of this change for cellular and cell based gene therapy products should be added to the table, or denoted that it is not reportable using a risk-based approach.
Page 24, row 3, column 1:	The text outlined under "Special Considerations" implies that changes in process parameters may have different reporting requirements based on impact. However, this table can be interpreted that all changes are PAS.	BIO believes that at a minimum clarity should be provided in this table (either within the row or as a footnote) that changes may be submitted under multiple reporting categories depending on the impact of the change. Ideally, examples of changes that fit each category should be provided within the table.
Page 24, row 3, column 1:	The Draft Guidance classifies a change in process parameter(s) monitored at critical steps outside of the range validated as a PAS.	BIO notes that the safety, quality, integrity, purity, and potency (SQIPP) impact should be taken into consideration and the classification could be downgraded based on this additional information.
Page 25, row 2, column 1:	The Draft Guidance classifies a change in CSS for storage and/or shipping of an intermediate as a PAS.	BIO asks FDA to clarify the following: • What change in dimension and/or shape is considered significant for PAS reporting and, if the change can be down-graded if it can be

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		demonstrated that the initial validations are not impacted by the change in size or material • If a storage time is considered • If this applies to all drug substance and intermediate steps or only after purification/sterile filtration
Page 25, row 4, column 1 and column 3:	Replacement of an in-house method with a compendial method, with no change in acceptance criteria, should be an AR as it is low risk and a method recognized by Health Authorities. Adding a test with superior performance, when done as part of technology improvement rather than in response to issues, could be CBE30.	BIO suggests editing column 3 (AR) to read: "Replacement of an in-house method with a compendial method, with no change in acceptance criteria."
Page 25, row 4, column 1:	The Draft Guidance discusses change in the drug substance or drug product release specifications.	BIO asks FDA to clarify whether this also applies to intermediate release specifications.
Page 25, row 4, column 2:	The Draft Guidance classifies relaxation of acceptance criteria to comply with a compendial test as a CBE30.	BIO asks FDA to clarify if this applies to acceptance criteria for starting materials and/or excipients.
Page 25, row 5, column 3:	The Draft Guidance discusses minor modifications to analytical procedure. BIO believes that additional detail around what qualifies as a minor modification would be helpful.	BIO suggests FDA clarify what qualifies as a minor modification to an analytical procedure and provide a few examples. Alternatively, BIO suggests that the Draft Guidance incorporate CDER language: "Change in the regulatory analytical procedure if the acceptance criteria remain unchanged and the

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		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 to have or is represented to possess."
Page 26, row 2, column 1:	The Draft Guidance lists replacing critical test control(s) or reagents as a PAS.	BIO suggests that this could be a CBE30 if data are generated to confirm no impact to the sensitivity or potency determination of the method. As such, we suggest moving this to column 2 (CBE30) and editing the text to read: "Replacing critical test control(s) or reagents (e.g., positive controls, capture antibodies, etc.) ~~without an approved protocol~~ with qualification data confirming the change in critical reagent had no impact on the sensitivity or accuracy of the method."
Page 26, row 4:	General clarification regarding reference standards.	BIO asks FDA to clarify if this refers to all reference standards regardless of which process step is being tested and the purpose of the test (introduction of and extension of shelf life).
Page 26, row 5, column 1 and 3:	The Draft Guidance uses the term "reference panel (panel member)" but it is unclear what this is.	BIO asks FDA to include a definition for "reference panel (panel member)" in the glossary and clarify in this section.
Page 26, row 6, column 3:	Changing from an in-house reference standard to a recognized national or international standard poses much less risk than moving from a recognized standard to an in-house standard and thus should have a lower reporting requirement.	BIO suggests editing the text in column 1 (PAS) to read: "Changing ~~from~~ to ~~a national or international reference standard to~~ an in-house reference material

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		from a national or international reference standard ~~and vice versa~~." And adding text in column 3 (AR) to read: "Changing from an in-house reference standard to a recognized national or international standard."
Page 26, row 7, column 1:	Changing between recognized standards is low risk and should have the same reporting category, AR, as for other biologics covered in this guidance.	BIO suggests editing the text to read: "Changing from a national to an international reference standard and vice versa. ~~NOTE: This applies only to vaccine, and cellular and gene therapy products.~~"
Page 27, row 4, columns 1 and 3:	BIO notes that some reference standards have a "retest date" rather than a shelf-life.	BIO asks FDA to clarify if re-test date is assimilated to a SL for the Agency and if an extension of re-test date falls under the same classification category.
Page 27, row 4, column 3:	As a secondary reference is validated against a calibrated reference and that the criteria taken into account for the validation of the secondary reference will be described in the file, the classification of such change is proposed to be notified via AR.	BIO suggest adding the following as an AR: "Classification of change for secondary reference derived from a primary USP/EDQM reference."
Page 27, row 6 column 1:	As written, this implies that all CCS changes are PASs, with the change in contact material and dimensions as examples. As this Guidance allows for changes to CCS to be lower reporting categories, the intention appears to be that these two issues would result in a prior approval changes.	BIO suggests editing the text to read: "Adding or replacing a primary CCS for storage and/or shipping of Drug Substance ~~including~~ with high potential to impact product quality which include a change in the product-contact material ~~or dimensions (size and shape)~~."

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	Further, a change in dimensions does not have a high potential to impact product quality.	BIO also suggests that a change in dimensions could be reported in a lower category (e.g., in an AR).
Page 27, row 6 column 3:	The Draft Guidance implies disposable bags to be higher risk than other DS containers, which is not always the case.	BIO suggests editing the text to read: "Change in a supplier of a primary CCS ~~(other than disposable bag)~~ with no change in the product-contact material." Additionally, we suggest instead of creating separate change reporting criteria for disposable bags, consider providing separate guidance with expectations/points to consider when using disposable systems.
Page 27, row 7 column 3:	BIO believes that as written, it is unclear what "bioburden-controlled DS" means.	BIO asks FDA to provide clarification for the term "bioburden controlled" or the text should be stricken.
Page 28, row 2, column 1:	The Draft Guidance includes change in the shipping conditions as a PAS. However, this change when shown by qualification data to have no impact to the product, should not require a PAS.	BIO suggests moving this from column 1 (PAS) to column 2 (CBE30) and editing to read: "Change in the shipping conditions (e.g., temperature, duration, packaging, etc.) with qualification data showing no impact on product quality ~~without an approved shipping protocol~~."
Page 28, row 5, column 1:	The change in the post-approval stability protocol or stability commitment doesn't explicitly state if it also covers changes in the protocols for commercial stability.	BIO asks FDA to clarify if changes in protocols for commercial stability are encompassed in this section.
Page 28, row 5, column 1:	The Draft Guidance discusses changes in post-approval stability protocol or stability commitment.	BIO believes that a deletion of a timepoint within the approved shelf-life may not impact the quality or

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		safety of the product and could be handled via an Annual Report, as appropriate.
Page 29, row 7 column 1:	New filling lines if identical or highly similar to the current fill line pose less of a risk to product quality and should be a lower reporting category. The note states that convenience kits and commercial diluents are excluded from this reporting category but does not provide what level of reporting is require if any.	BIO suggests editing the text of column 1 (PAS) to read: "Change (e.g., new manufacturer, new location, ~~new filling line,~~ change in sterilization method/cycle) in the diluent co-packaged with the product. NOTE: This does not apply to convenience kits or commercially available diluents which are not reportable." and adding text in column 2 (CBE30) to read: "New filing lines, in the same facility that are identical or highly similar to the current filing line."
Page 29, row 5, column 2:	A change in fill volume is categorized as a CBE30 but it is unclear if this refers to the labeled volume as opposed to the target fill volume/range.	BIO asks FDA to clarify whether this applies to labeled volume only or also to fill volume/range.
Page 30, row 4:	BIO suggest adding an additional item under "Description of Manufacturing Process and Process Controls."	BIO suggest adding the following to column 2 (CBE30): "Scale-up of the manufacturing process at the formulation/filling stage provided: 1. The proposed scale uses similar/comparable equipment to that approved (N.B. change in equipment size is not considered as using similar/comparable equipment).

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		2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized). 3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns. 4. No change in the principle of the sterilization procedures of the drug product."
Page 30, row 4:	This section covers "Description of Manufacturing Process and Process Controls."	BIO suggests adding an item discussing the opportunity for a Sponsor to provide a protocol for reworking.
Page 30, row 4:	BIO suggests adding an additional item under "Description of Manufacturing Process and Process Controls."	BIO suggests adding the following to column 3 (AR): "Addition of an IPC."
Page 30, row 4:	BIO suggests adding an additional item under "Description of Manufacturing Process and Process Controls."	BIO suggests adding the following to column 3 (AR): "Tightening of IPC acceptance criteria."
Page 30, row 4:	BIO suggest adding an additional item under "Description of Manufacturing Process and Process Controls."	BIO suggests adding the following to column 3 (AR): "Change from manual to automated inspection."
Page 30, row 5 column 1:	As written "change in unit operations" is vague and implies all changes are a PAS which is contradictory to other changes identified in this Draft Guidance. As such BIO suggests writing as a more affirmative, clear statement.	BIO suggests editing the text to read: "Change in ~~unit operations and their~~ the sequence of unit operations, ~~including~~ addition, deletion, or substitution of unit operation(s)"

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Page 30, row 4:	Scale-up at the formulation and filling stages, if within the validated aseptic time, could have a lower quality risk and should have lower reporting category than freeze-drying scale-up.	BIO suggests including multiple reporting categories for this change depending on the potential impact of the change on product quality (based on validated aseptic time etc.). [See BIO's suggested line edit for page 30, row 6, column 1 for example.]
Page 30, row 6 column 1:	Scale-up at the formulation and filling stages have a low risk to impact the quality of the product provided and should be lower reporting category.	BIO suggests editing the text of column 1 to read: "Scale-up of the manufacturing process at the ~~formulation/filling/~~lyophilization stage." And adding text in column 3 for AR changes to read: "Scale-up at the formulation and filling stages that are within the validated aseptic processing time."
Page 30, row 7, column 3:	The Draft Guidance classifies reprocessing in the manufacture of Drug Product with an approved reprocessing protocol as an AR.	BIO believes that batches reprocessed in accordance to an approved protocol that has been validated should not be reported to FDA. This should be controlled via the firm's quality system as it's already been shown to not impact product quality, etc. As such, BIO suggest deleting this.
Page 31, row 3 column 1:	The text outlined under "Special Considerations" implies that changes in process parameters may have different reporting requirements based on impact. However, this table can be interpreted that all changes are PAS.	BIO suggests that at a minimum, clarity should be provided in this table (either within the row or as a footnote) that change may be submitted under multiple reporting categories depending on the impact of the change. Ideally, examples of changes that fit each category should be provided within the table. Additionally, BIO suggests editing the text to read:

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		"Change in the CCS used for storage and/or shipping of a stored intermediate that includes a change in the product-contact material or dimensions (size and shape) which has the potential to have an adverse effect on product quality."
Page 31, row 5	BIO suggests adding additional examples in the control of excipients section.	BIO suggests adding the following examples in this section in column 3 (AR): "Changes in an excipient supplier without any changes to the quality attributes of the excipient." "Changes related to control of excipient in connection with pharmacopeia changes."
Page 32, row 2 column 3:	Changes in the source of a compendial-grade excipient is low risk as any source is required to meet the same standards, as such this change should also be an AR.	BIO suggests editing the text to read: "Change in the supplier of an excipient with no change in the source or change in the supplier of a compendia grade excipient regardless of source." BIO also asks FDA to clarify if this classification also applies to a change in source of excipient.
Page 32, row 6 column 1:	As written, this implies that all CCS changes are PASs, with the change in contact material and dimensions as examples. As this Draft Guidance allows for changes to CCS to be lower reporting categories, the intention appears to be that these two issues would result in a PAS. Further, a change in dimensions does not have a high potential to impact product quality.	BIO suggests editing the text to read: "Adding or replacing a primary CCS for storage of Drug Product which includes ~~including~~ a change in the product-contact material ~~or dimensions (size and shape)~~." Further, BIO suggests that a change in dimensions could be reported in a lower category (e.g., in an AR).

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Page 32, row 6 column 1:	The Draft Guidance currently categorizes adding or replacing a supplier for components of the CCS that are supplied as ready to use/sterilize as PAS. In addition, adding or replacing location that performs depyrogenation or sterilization for components of the CCS that are supplied as ready-to-use or ready-to-sterilize without a change in supplier, product contact material, or dimensions is categorized as CBE30.	BIO asks FDA to clarify if this classification only applies to final containers and also if this applies to sites under a supplier's responsibility. Additionally, we ask FDA to verify if the supplier name is to be reported in 3.2.P.7. and to specify requirements to these categories or give examples of supportive documentation required from the supplier and/or manufacturer to support the change.
Page 32, last row column 1 and 3 (through page 35 where applicable):	BIO suggests adding delivery system after CCS to include delivery devices.	BIO suggest editing the applicable text to read: "primary CCS and/or delivery system"
Page 34, row 4 column 3:	This description is vague as "CCS" can refer to either the primary, secondary and tertiary packing (shipping containers/materials). Changes the in primary CCS and shipping is documented elsewhere in this Guidance as such this seems to imply changes in secondary packaging.	BIO suggests editing the text to read: "Change in ~~the CCS for storage and shipping~~ functional secondary packaging of Drug Product. ~~with no change in the product contact material and dimensions (size and shape).~~"
Page 35, row 5:	BIO suggests adding an additional example in the equipment section.	BIO suggests adding the following example in this section in column 3 (AR): "Changes -- like-for-like, computer system, SOP -- to quality control (QC) equipment."
Page 36, row 2 column 2:	BIO believes that if the equipment is similar and there is no change to methodology, or process	BIO suggests moving the text from column 2 (CBE30) an adding the following text to column 3 (AR):

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	parameters, this risk to impact product quality is low and the change should be annual reportable.	"If the equipment is similar and there is no change to methodology, or process parameters, this risk to impact product quality is low and the change should be annual reportable." Additionally, we ask FDA to clarify if a change to a newer model of the same equipment is in scope as well as if all equipment is in scope or only equipment deemed critical to the process.
Page 36, row 6 column 3:	BIO believes that the term "approved facility" is vague. As such we suggest clarifying with similar language used for the change in row 7 on this page.	BIO suggests editing the text to read: "Addition of packaging and/or labeling lines to ~~an approved facility~~ a facility with an active CGMP status (has an acceptable inspectional history)."
Page 37, row 2:	As proposed, for testing site changes there are various filing mechanisms described however it is unclear if the principles of PAC-ATLS be applied.	BIO asks FDA to confirm whether the principles of PAC-ATLS should be applied.
Page 37, row 3 column 1:	BIO believes that this change is of moderate risk and should be reported as a CBE30. This is consistent with guidance for specified biologics and previous guidance for non-specified biologics.	BIO suggests moving the following text from column 1 (PAS) to column 2 (CBE30). "Addition or replacement of a testing laboratory that performs critical testing with a new testing laboratory at a new location. Examples would include potency or safety testing for the final drug product."
Page 37, row 3 column 2:	BIO believes that this is a low risk change and should be classified as annual reportable.	BIO recommends moving the following text from column 2 (CBE30) to column 3 (AR): "Addition or replacement of a testing laboratory for

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		release or stability testing by moving within an existing location."
Page 37, row 7 column 2:	BIO believes that this change is low risk and should be classified as an AR.	BIO suggests moving the following text from column 2 (CBE30) column 3 (AR): "Addition or replacement of an existing suite/room that does not affect sterility assurance or contamination/cross-contamination within an approved manufacturing building."
Page 38, row 2, column 3:	The Draft Guidance classifies a change in a location or modification to areas used in support operations as an AR.	BIO asks FDA to clarify if a QC testing lab is considered a support operation.
Page 38, row 4 column 3:	A change in environmental quality classification to a lower classification except for aseptic processing areas is categorized as AR.	BIO asks FDA to clarify if downgrading of bulk manufacturing areas (fermentation, purification) from grade B to C that are claimed bioburden controlled instead of aseptic areas is within the scope for AR changes.
Page 38-39, column 3:	Installation of new HVAC system or modification to environmentally controlled areas used for process steps is considered AR change except for aseptic areas but unclear of the category for aseptic changes.	BIO asks FDA to clarify if the exception means that the next higher category will then apply for aseptic area.
Page 39, row 6 column 2:	BIO believes that this change is low risk and should be classified as an AR.	BIO suggests moving the following text from column 2 (CBE30) column 3 (AR): "Use of an alternate filling line approved for aseptic manufacture of other products with no change in the

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		validated aseptic process and product contact equipment."
Page 40, table footnotes:	BIO believes that these changes are low risk and have minimal potential to impact product quality and should be reported in an AR which is consistent with other guidance.	BIO suggests moving the changes noted in the footnotes to above table as AR changes.
Page 40, table footnotes:	It is unclear if the cGMP status must be from the FDA. The Draft guidance reads that "addition or replacement of an existing labeling/packaging location that has a CGMP status…the FDA recommends that the following manufacturing changes be submitted in a CBE supplement under 21 CFR 601.12(c)(5)."	BIO asks FDA to clarify if the CGMP status can be from an authority other than FDA.