December 13th, 2021

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

Re: Docket No. FDA–2021–D–1047: Q13 Continuous Manufacturing of Drug Substances and Drug Products; International Council for Harmonisation; Draft Guidance for Industry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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the ICH Draft Guidance *Q13 Continuous Manufacturing of Drug Substances and Drug Products* (Draft Guidance or Guidance).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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates this opportunity to submit comments regarding the ICH Draft Guidance *Q13 Continuous Manufacturing of Drug Substances and Drug Products.* Specific, detailed comments are included in the following chart.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/
Katherine Donigan, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
PART I: CONTINUOUS MANUFACTURING OF DRUG STUBSTANCES AND DRUG PRODUCTS		
1. INTRODUCTION		
1.2 Scope		
Lines 14-15	Some ATMP manufacturing processes can fall into the definition of CM. Although not explicitly excluded from this guidance, it is not clear if they would be understood as part of biological/biotechnological entities.	BIO asks the Agency to clarify if principles can also apply to ATMP.
Lines 15-15	What is meant by "other biological/biotechnological entities"? The prior definition of therapeutic proteins appears broad enough.	We ask the Agency to please provide clarification or consider removing.
Lines 19-20	The unit operation is perfusion, not "perfusion bioreactor".	We recommend editing the text to read: “While this description may apply to an individual unit operation (e.g., tableting, perfusion ~~bioreactors~~)…”
2. CM CONCEPTS		
2.2 Batch definition		
Lines 52-64	The need to "define" a batch is not questioned, and the possibility of defining it according to time or other sound approach is supported. However, there may be situations where the defining it by "size" may not always be the most relevant, e.g., yield/productivity or flow rate may not always be constant leading to a fairly wide range of "batch sizes".	BIO suggests that while definition by size is most common, the text should keep open other possibilities.
3. SCIENTIFIC APPROACHES		
3.1 Control Strategy		
Lines 70-81		We request that the Agency include an example of state of control in the Annex. This would be helpful for demonstrating when a state of control has been achieved.

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Lines 100-101	The word confirmation used in both phrases "Appropriate methodologies (e.g., RTD studies, in silico modeling with experimental confirmation) should be used…" and "…in silico modeling with experimental confirmation…" suggests that experimental "confirmation" always needs to take place as part of using an in silico model, which can be unnecessarily restrictive or unduly burdensome if the model is validated to a sufficient level of rigor. Model validation needs to take place, confirmation of a model prediction post validation may not be needed.	We recommend editing the text to read: "Appropriate methodologies (e.g., RTD studies, in silico modeling, and experimental ~~confirmation~~ runs) should be used…"
Lines 108-109	Delete the word "small from this sentence, as the step change size depends on the process and formulation.	We recommend editing the text to read: "Step testing by making small changes to the quantitative composition of the process stream (e.g., ~~small~~ increments of a constituent) …"
Lines 124	Remove "process" since the point is about the drug substance, not a process.	We recommend editing the text to read: "For a chemically synthesised drug substance ~~process~~, viscosity, concentration, …"
Lines 154-157	These statements are conjecture and do not hold true for all processes.	BIO recommends removal of this entire paragraph.
Lines 156	If this paragraph is not deleted as we suggest, please add "synthetic" prior to "drug substance".	We recommend editing the text to read: "For example, in a drug substance ~~process~~, reactor design can…"
Lines 207-208	Editorial: "Through use of in silico experimentation, process models also enhance process understanding and can reduce the number of experimental studies." "In silico experimentation" is a "niche" term used predominantly in the domain of computational biology, and not widely used in other domains, particularly our industry. The fragment "through use of in silico experimentation" (i.e., through simulation or computer	We recommend editing the text to read: "~~Through use of in silico experimentation,~~ P~~p~~rocess models can ~~also~~ enhance process understanding and ~~can~~ reduce the number of experimental studies."

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	simulations) does not add much to the sentence, thus an alternative wording is recommended.	
Lines 219-220	"…and relevant data are needed to select model inputs and model-governing equations." This assumes that the model is equation-based, which is not the case for data-driven or mechanistic (hybrid data-driven equation-based) models. The terminology "model formulation" is more widely used and accepted, and it encompasses all types of models.	We recommend editing the text to read: "Risk assessments, sound scientific rationales, and relevant data ~~inform the selection of model inputs and model-governing equations~~ are needed to select model inputs and model formulation."
Line 233	Is there any dependence on the use of the model, e.g., if the model were used only as part of process development, is there a need for continued assessment of model performance?	BIO requests clarity if this is not applicable to every model used.
3.2 Changes in Production Output		
Line 240	Suggest removing "output" from the section heading. It might be clearer to have a section discussing changes in the process; much of this is relevant to process changes regardless of the impact on output levels - and assessment of potential impact to output quality is relevant to every process change.	We recommend editing the section heading to read: "Changes in Production ~~Output~~"
3.3 Continuous Process Verification		
Line 285	"…soft sensors and models." In the Glossary, a soft sensor is defined as a model; use of "soft sensors and models" appears redundant.	We recommend editing the text to read: "…as in-line/online/at-line monitoring and control, and soft sensors ~~and models~~."
4. REGULATORY CONSIDERATIONS		
Entire Section		
	ICH Q13 Step 2 increases expectations for reporting control strategy elements that have been traditionally managed within the quality system (e.g., sampling	We recommend sections that should be revised include 4.1 Process descriptions, 4.2 Control strategy, 4.7 Process validation, and Table 1.

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	plans, in-process controls, and models). These elements should be considered PQS matters and not be considered established conditions that require regulatory reporting if changed. Increasing the level of detail for continuous manufacturing relative to traditional technology will discourage adoption of the technology as it would lead to a high number of supplements/variations worldwide and could increase supply chain complexity and vulnerability.	
4.1 Process Description		
Lines 294-298	It would be valuable to acknowledge CM processes (e.g., ATMP) where there is no real DS step (i.e., the process runs from SM to DP without interruption). This may help to avoid to have DS arbitrarily defined for regulatory purposes.	
4.2 Control Strategy		
Lines 342-343	We recommend adding "as appropriate" to this sentence. The list of important aspects to be included in the marketing application seems excessive and should only be added as needed based on the overall strategy. For instance, sample size and frequency likely could be managed at the site under the PQS in many instances.	We recommend editing the text to read: "Other important aspects should be defined, as appropriate, such as the sampling strategy…"
Line 370		We recommend that the Agency include the definition of "RTRT" in the glossary or refer to the definition in ICH Q8(R2).
4.3 Batch Description		
Lines 399-402	It would be valuable to get more recommendation on how batch definition could be based on sublots and or pooled sublots.	

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SECTION	ISSUE	PROPOSED CHANGE
Lines 404-405	What is the purpose of defining an intended batch size before start of manufacturing? One significant advantage of continuous manufacturing is NOT being bound to batch size, so why introduce it here?	We suggest that PQS should describe start-up, ramp-down and steady state maintenance of the process.
4.5 Drug Substance and Drug Product Stability		
Lines 417-418	CRITICAL: This sentence causes confusion and may be overly restrictive. The subsequent paragraph explains quite well on how to handle PSB batches and a cross-reference to 3.2 should not be needed.	We recommend removing the following sentence: ~~"See Section 3.2 for considerations that should be taken into account if production output between stability and commercial batches is different".~~
4.6 Conversion of a Batch Process to CM		
Lines 436-437	It is implicit that any process change out of the regulatory file will require regulatory approval prior to implementation.	We recommend removing the following sentence: ~~"Manufacturers should seek regulatory approval before the conversion of an approved batch process to a CM process."~~
Line 440	CRITICAL: Add a general statement to confirm that an active market authorization could allow supply of drug substance through either batch or CM process; this should be viable as long as product comparability has been adequately demonstrated.	We recommend adding the following sentence to end of section 4.6: "Demonstration of product comparability could enable supply of drug substance and drug product by both batch and CM processes."
4.7 Process Validation		
Lines 441-456	Process validation section could provide some recommendation on considerations on variability occurring during the process, e.g., yield, glycosylation in perfusion bioreactor	
Lines 448-449	As written, it would appear that continuous process verification would require an end-to-end continuous process. It is unclear how this sentence would apply to a CM process which has some batch unit operations.	
4.10 Submission of CM-Specific Information in the CTD		

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Line 480	Some of what is included in Table 1 is not CM-specific information.	BIO recommends either including only CM-specific information or changing this to be more comprehensive for all the sections.
Line 480	Under "Manufacturing and Process Development" in Table 1: Some companies include some of this type of information in the process validation sections, instead of process development (process validation is not only PPQ). This guideline could limit the flexibility for what is considered validation and included in those sections.	We suggest indicating that some of this could be included as PV.
Line 480	Under "Controls of Critical Steps and Intermediates" in Table 1: Are validation data and a maintenance protocol needed only for high-impact models, or could these also be necessary for some other models (particularly medium-impact)?	BIO recommends considering whether this is only relevant for high impact and potentially clarifying. (Same comment for "Description of Manufacturing Process and Process Controls" section in this table.)
5. GLOSSARY		
Entire Section		We recommend including the definition of “State of Control” in the Glossary.
Line 511	Remove reference to 'EP'. The reference is too general and does not add value.	We recommend editing the text to read: “…potentially correlated variables. ~~(EP)~~”
PART II: ANNEXES		
ANNEX I: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES FOR CHEMICAL ENTITIES		
1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW		
Line 592	The text notes that Figure 1 is not intended to represent a regulatory flow diagram. What are the expectations for a flow diagram in a regulatory filing?	BIO requests that the Agency provide an update to Figure 1 to represent a regulatory flow diagram to serve as an example for authors.
2. CONTROL STRATEGY AND OTHER TECHNICAL CONSIDERATIONS		
2.1 Equipment Design and Integration		
Line 622	Given the long processing time up to months, it would be useful to discuss how the carbon filtration was handled over time. Were there replacements required?	

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2.4 Process Validation		
Line 720	This process employs a long run time of several months (line 701). Description of how batch sizes and durations where primary stability batches were handled would be a useful example to the concepts described in section 4.5.	
ANNEX II: CONTINUOUS MANUFACTURING FOR DRUG PRODUCTS		
1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW		
Lines 752-759		BIO requests that the Agency provide an update to Figure 2 to represent a regulatory flow diagram to serve as an example for authors.
2. CONTROL STRATEGY AND OTHER TECHNICAL CONSIDERATIONS		
2.1 Material Characterization and Control		
Line 796	Editorial: "Modelling", uses British spelling, where American spelling has been used throughout the document.	We suggest the Agency consider using "Modeling".
2.4 Process Validation		
Lines 851-853	It is stated earlier in the section that the batch size of this process is defined by run time at a predefined mass flow rate to achieve drug product batch size between 360 and 1080kg.	We ask that the Agency please clarify continuous process verification approach. Description of how the run time extensions beyond current experience were validated would provide a great example.
ANNEX III: CONTINUOUS MANUFACTURING OF THERAPUETIC PROTEIN DRUG SUBSTANCES		
1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW		
Lines 864-983	Annex III contains guidance-like language related to expectations for continuous manufacturing for therapeutic proteins and does not read like an example.	BIO recommends replacing “should” with “was” or “were” to make it a true example rather than regulatory expectations (i.e., lines 894, 898, 902, 907, 910, 913, 915, 918, 925, 950, 970, 973, 975, 976). Alternatively, the essential aspects that constitute regulatory expectation should be moved into the core document.

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SECTION	ISSUE	PROPOSED CHANGE
2. CONTROL STRATEGY		
2.2 Equipment Design and System Integration		
Line 919	The wording "inadvertent contamination" is superfluous.	We recommend editing the text to read: …" detection of ~~inadvertent~~ contamination, …"
Lines 923-924	The phrase, "between steps such as virus inactivation" is an incomplete example.	We recommend editing the text to read: "between ~~steps such as virus inactivation~~ unit operations…"
Lines 927-929	With this formulation, physical segregation (in case of open handling) would be required only downstream of the virus filtration step? i.e., process steps upstream of virus filtration could be open and without physical segregation?	
3. PROCESS VALIDATION		
3.2 Run Time Considerations		
Line 966	Reference to ICH Q5B and D should be considered.	
ANNEX IV: INTEGRATED DRUG SUBSTANCE AND DRUG PRODUCT CONTINUOUS MANUFACTURING		
1. INTRODUCTION		
Lines 984 – 1149	Annex IV contains guidance-like language related to expectations for integrated continuous manufacturing and does not read like an example.	BIO recommends replacing "should" with "was" or "were" to make it a true example rather than regulatory expectations (i.e., lines 1026, 1073, 1079, 1084, 1086, 1092, 1095, 1099, 1100, 1111, 1117, 1137). Alternatively, the essential aspects that constitute regulatory expectations should be moved to the core document.

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