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Overview of comments received on ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products (Step 2) (EMA/CHMP/ICH/427817/2021)

Please note that comments will be sent to the ICH Q13 EWG for consideration in the context of Step 2 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	0	0		The document reads well, the concepts and ideas all make sense and are aligned with the BioPhorum thinking on continuous manufacturing of drug substances and drug Products.	
BioPhorum	0	0		Our feedback reflects our main interest that is continuous processing for biomanufacturing. In that way, the document describes processes that are end-to-end continuous, the reality is however more complex than this (especially for biologics), where processes are a mix of batch and continuous steps. The concepts and principles of the guideline are directely relevant to NCEs, some would be different from biologics. However, currently this is not covered.	
BioPhorum	0	0		The biologics example in the appendixes is considered weak, as it only contains aspirational statements and as such, does not provide a real example, contrary to the other appendixes. Industry recognizes that continuous processes for the manufacture of biologics have not been filed yet, which makes the description of an example by the committee difficult. However, industry is actively working on this and would be delighted to explore with the committee one of the most mature examples, continuous perfusion at a scale of 500 L, even if this process has not reached the filing stage yet.	
BioPhorum	0	0		A definition section comprising of 'residence time distribution' and 'processing time' would be useful, as this is currently not clear in the document that uses the two terms.	
BioPhorum	0	0		Definitions and principles should be aligned to those already developed by industry and documented for example in the ASTM standards for continuous processing	
BioPhorum	0	0		In its comments, the BioPhorum team refers to **Process fatigue**: this is a concept that refers of equipment wear and tear and changes that may occur to the processes that are run for extended periods of time, when compared to a batch process (such as conversion of phenotypic populations in a bioreactor). From a consumable's perspective, it also includes getting closer to points of failure. It is expected that the principle of process fatigue is examined as part of the batch process conversion or design of a new continuous process	
International Society for Pharmaceutical Engineering (ISPE)	0	0		The document is scientifically sound and well-structured with accurate and concise descriptions of aspects related to continuous manufacturing and good examples covering drug substance (DS) and drug product (DP) for both small molecules and large molecules. However, from a regulatory perspective, some of the content could be interpreted as overreaching in its expectations for what should be reported vs. what has been traditionally part of the quality system.	
International Society for Pharmaceutical Engineering (ISPE)	0	0		Reference to annexes I through III is not made inside the guideline main body, while IV and V are.	It is recommended to include a final paragraph after Table 1 and before the Glossary that references those annexes.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	0	0		The term “process dynamics” is used incorrectly throughout the document and often interchangeably with residence time distribution (RTD). Technically, a system only has process dynamics when it is changing and not when at steady state. In contrast the residence time distribution is present, even when the system is not dynamically changing.	Please revise the document appropriately (i.e., lines 89, 90, 92, 99, 190, 195) to correctly capture this concept.
EuropaBio	0	0		Discussions around funnel plots appear to suggest that funnel plots cannot be used as a primary control method. However this should be an option (e.g. an alternative to NIR) when suitably justified.	
EuropaBio	0	0		previous version of the draft where BIO provided comments - 261 (Section 4.1) - Recommend to also consider addressing PAT models. Rationale: PAT models are integral to CM processes.	At a minimum add reference to other guidelines on PAT models
EuropaBio	0	0		previous version of the draft where BIO provided comments - 846-848 (Annex II) - This section implies the listed characterisitics should be evaluated for all materials. The section should be softened to state relevant tests should be performed as appropriate based on the risk assessment. Risk assessment can be used to justify low impact for some material properties.	These material attributes include…….and they should be characterized using appropriate methods as appropriate based on the risk assessment.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	15	15	1.2	What is meant by "other biological/biotechnological entities"? The prior definition of therapeutic proteins appears broad enough. Rationale: column "Proposed changes / reccomendation"	**Please provide clarification or consider removing.**
BioPhorum	19	21		Although the process flow in Figure 1 could be possible, upon further review there are a few elements which do not fully reflect the current thinking and more common practice for how such a system would be more likely designed. Edits are suggested to both update the figure/process description and simplify the example. These do not impact the explanation of related principles from the main guidance. A simpler process will allow additional focus on the more important aspects of the application of the guidance, rather than any questions or uncertainty on the process details. See column "Proposed changes / reccomendation" +17:23	This guideline focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected." (Remove first phrase, starting with "While....may apply...."
EFPIA	19	20	1.2	Editorial. Remove "bioreactors". Rationale: Column "Proposed changes / reccomendation"	**The unit operation is perfusion, not "perfusion bioreactor".**
APIC	19	21	1.2	The information in this guideline should be as concise as possible. The first phrase in the following text is unnecessary. "While this description may apply to an individual unit operation (e.g., tableting, perfusion bioreactors), this guideline focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected."	Change please to: "This guideline focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected." (Remove first phrase, starting with "While....may apply...."
BioPhorum	21	23		The original sentence implies that there will be a direct and immediate impact, but that may not be the case	In this context, any changes made in a unit operation of CM should be evaluated in regards to the potential impact on downstream and upstream (e.g., via a feedback control) unit operations
EFPIA	21	22	1.2	In this context, any changes made in a unit operation of CM may have a direct and often immediate impact on downstream and upstream (e.g., via a feedback control) unit operations, This sentence implies that there will be a direct and immediate impact, but that may not be the case.	Here is the proposed text change please: **"In this context, any changes made in a unit operation of CM should be evaluated in terms of the potential impact on downstream and upstream (e.g., via a feedback control) unit operations."**
APIC	21	22	1.2	This sentence implies that there will be a direct and immediate impact, but that may not be the case. "In this context, any changes made in a unit operation of CM may have a direct and often immediate impact on downstream and upstream (e.g., via a feedback control) unit operations." I proposed a change in text.	Here is the proposed text change please: "In this context, any changes made in a unit operation of CM should be evaluated in regards to the potential impact on downstream and upstream (e.g., via a feedback control) unit operations."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	23	23	1.2	The scope of the document should clearly identify that the additional requirements for CM in hybrid processes do not apply to the batch manufacturing portions of the hybrid process. For example, in batch manufacturing processes, IPC sampling frequency / location may not be supplied in the CTD and there is no specific diversion strategy for a portion of a batch.	Propose adding additional sentence for clarity at the end of the paragraph. A**dditional requirements discussed in this guideline only apply to the CM portions of hybrid processes; follow applicable ICH guidelines for batch manufacturing requirements.**
APIC	29	30	1.2	This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The examples and approaches described in these annexes are not exhaustive, and alternative approaches can be used."	Change please to: "The examples and approached described in these annexes are mock examples provided for illustrative purposes. They only suggest how this guideline could be applied, and should not be used as a template or the sole basis for a regulatory submission." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)
BioPhorum	30	32		This is the language used for other ICH annexes, specifically ICH Q12. Please align	The examples and approaches described in these annexes are mock examples provided for illustrative purposes. They only suggest how this guideline could be applied and should not be used as a template or the sole basis for a regulatory submission.
EFPIA	38	39	2.1	An additional bullet point could be added for clarity to cover the concept of intergrating automized batch unit oprerations with fully continuous unit operations, thereby creating an overall continuous output mode. This way of operation could be relevant in starting material preparations, intermediate unit operations that are better in batch mode as well as for example automized isolation or drying operations for isolated APIs or intermediates. Current wording can be confusing. It refers to intergrating the batch operation only. The internt of the production line should be to include any systems where batch and continuous operations occur and are integrated under a single system.	**A manufacturing approach in which batch and continuous unit operations are integrated and operate as a system in a continuous mode. Reword first bullet point or add another bullet point.**
Gilead Sciences	38	39	2.1	Definition of integrated system/unit operations required	Define what is the difference between “integrated unit operations” and “unit operations operation in a continuous mode”
International Society for Pharmaceutical Engineering (ISPE)	39	39	2.1	Integration is not limited to continuously run unit ops. It can be achieved between a batch system with recycle (United State Pharmacopoeia perfusion) and a continuous system (Drug Substance Perfusion train).	batch mode while others ~~are integrated and~~ operate in a continuous mode
BioPhorum	49	50		Similar comment to line 19, it is valuable to define part of the process as a single unit i.e Bioreactor. More clarification on the thinking behind this would also be helpful.	Add - **A steady state operation in a continuous mode (e.g., Perfusion Bioreactor for the manufacture of a therapeutic protein drug substance)**
BioPhorum	51	64		More details are required for this section to reflect the suttleties of the definition of batch size and sizing of cycle. For example, 'the other considerations would benefit from practical examples such as based on the lifetime of a critical material - e.g viral filter lifetime, or a pre-defined criteria or target, as it is the case for cell cultures. Other runtime examples would also be helpful, not just mass flow rate.	
BioPhorum	60	61		The current paragraph does not provide clarification on whether the definition of a batch can be changed within a connected or continuous process. For example, in a biomanufacturing process, the upstream and dowstream processes may have different different batch definitions; is it permissible? Example in Annex 4 covers linked DS and DP with separate release criteria. Annex 3 (line 879) implies harvest is also a means to define the batch, so can a CM batch be divided into smaller units than just the whole?	
EFPIA	60	61	2.2	A single batch may be composed of several identical sub-cycles, which are composed of only a part of the total unit operations. The diversion of a sub-cycle, e.g., due to a technical failure, may however not impact the remainder of the sub-cycles or the predefined acceptance criteria. It should therefore be possible that the total batch yield may also be specified per cycle. ? DS filling inhomogeneity => some vessels to be discarded, but the remainder can be used? ? (Nano) Filter block triggers temporary material diversion until filter changed => total yield impacted, but not quality ?	Edits added to respective sentence in lines 60-61: **Other approaches to define batch size can also be considered, if scientifically justified based on the characteristics of the CM process, e.g., per identical sub-cycles.** **REQUEST EWG COMMENT**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	63	64	2.2	Lines 63-64 seem still on the definition of batch.	Move lines 63-64 before line 60
BioPhorum	67	69			The development of a successful control strategy for CM is enabled by a holistic approach, considering aspects specific to CM (discussed below), **including equipment and process fatigue** and the principles described in ICH Q8 -11.
EFPIA	73	73	3.1	Remove the word "some" before CM processes, Rationale: Column "Proposed changes / reccomendation"	It would be more clear to just use a terminology "controlled state" or "state of control" instead of "steady stade". From a strict technical perspective a complete steady state is never achieved, hence better to use controlled state.
EFPIA	77	81	3.1.1	CM operations afford additional opportunities for process monitoring and control that assure the process is operating in a state of control. Thus, CM does not require comparisons to historical ranges to identify drifts or trends within the batch to ensure the process is operating in a state of control. While this may be a best practice, written as is, this may be considered as a new requirement. Rationale: column "Proposed changes / reccomendation"	It is important to have mechanisms in place to evaluate the consistency of operation and to identify situations in which parameters are within the specified range yet outside historical operating ranges, or they are that showing drifts or trends.
BioPhorum	79	81			operating ranges, or they are showing drifts or trends. **Mechanisms should also be in place to identify whether the drifts or trends originate from variation of the inputs to the process step or are due to equipment or process fatigue. For example, in a biologic process, a change in the absorbption profile of the elution may be due to resin aging or the input changing.**
BioPhorum	87	87			Add **Transient events can be defined through time, process parameter and quality attibute values**
EFPIA	89	679	Multiple	Per the definitions in the glossary, process dynamics is related to changes/disturbances during CM processing, whereas RTD exists at all times, including during steady state operations. Thus they are not fully interchangeable terms but are used this way. To ensure accurate and consistent use of the terms across the industry, the attached word document outlines proposed changes to better align with the definitions. Additionally a definition is proposed for mean residence time. See attached word document in Column "Proposed changes / reccomendation" . The following defintion is suggested for mean residence time in line with ASTM 2968-14. Mean Residence time—the average time that process material is in a specific process environment/vessel/unit operation.	 PROPOSED EDITS FOR ALL
Gilead Sciences	89		3.1.2	Too many places calls out RTD. Do studies with RTD characterize a flow reactor system, simple or complex? If so, modify the wording in line 89 to reflect this idea.	
EFPIA	100	101	3.1.2	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. The model can be validated without being confirmed? What does confirmation mean? Confirmation is a nebulous term...	**Consider replacing with "Appropriate methodologies (e.g., RTD studies, in silico modeling, and model validation or experimental ~~confirmation~~ runs) should be used (...)".**
Gilead Sciences	104	108	3.1.2	Very descriptive wording for the requirement of tracer might make selection of tracer with special needs difficult.	Remove "For example, when conducting RTD studies, the tracer used to replace a constituent of the solid or liquid stream should have highly similar flow properties as those of the constituent replaced. A tracer should also be inert to the other components of the process and should not alter how processed materials interact with equipment surfaces"

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EFPIA	124	124	3.1.3	Editorial. Remove "process" since the point is about the drug substance, not a process. See column "Proposed changes / reccomendation"	**For a chemically synthesised drug substance ~~process~~, viscosity, concentration, or the multiphase nature (e.g., presence of solids) of the feeding solution may impact flow properties or conversion.**
Gilead Sciences	124		3.1.3	Not sure why presence of solids is called out for the multiphase nature. Feeding solution with two partially miscible liquids or gas-liquid system would have similar challenges.	Remove “e.g. presence of solids”
BioPhorum	128	130		The original sentence implies that the industry or drug manufacturing understanding and knowledge of their cell culture is not considered	For a therapeutic protein (e.g. monoclonal antibodies) process, **cell culture media and feed components should be characterized and understood regarding potential impact to cell culture performance. Requirements for raw material lot consistency, including cell culture media/feed, buffers, and other starting materials for the downstream CM process, should be adjusted based on prolonged run times of CM, as necessary**
EFPIA	128	132	3.1.3. Material Characterization and Control	This sentence implies that the industry or drug manufacturing understanding and knowledge of their cell culture is not considered: "For a therapeutic protein (e.g., monoclonal antibodies) process, the higher variability of cell culture performance. Prolonged run times may require different lots of media, buffers, or other starting materials for the downstream CM process, potentially introducing more variabilities to the process." I have proposed an update to the text. Rationale: Refer to Column "Proposed changes / reccomendation"	Please update text as follows: **"For a therapeutic protein (e.g. monoclonal antibodies) process, cell culture media and feed components should be characterized and understood regarding potential impact to cell culture performance. Requirements for raw material lots, including cell culture media/feed, buffers, and other starting materials for the downstream CM process, should be considered based on prolonged run times of CM, as necessary."**
Regeneron Pharmaceuticals, Inc.	128	132	3.1.3	**Referenced Line Excerpt:** *“For a therapeutic protein (e.g., monoclonal antibodies) process, the higher variability of feed stocks such as metal salts, vitamins, and other trace components may adversely impact cell culture performance. Prolonged run times may require different lots of media, buffers, or other starting materials for the downstream CM process, potentially introducing more variabilities to the process .”* **Regeneron Comment:** It is important to recognize that the variability in components such as metal salts, vitamins, and other trace components is often derived from starting materials such as media and buffers. Given this recognition, we believe that the above referenced excerpt would benefit from additional clarity by adjusting the structure and revising some of the wording to directly address the consideration that should be given to the use of different lots or types of media, buffers, and other starting materials. As such, we propose the revisions captured in the corresponding Proposed Changes/Recommendation column.	For a therapeutic protein (e.g., monoclonal antibodies) process, consideration should be given to the use of different lots or types of media, buffers, or other starting materials in a given unit operation and how these may influence process consistency and quality. For example, in cell culture unit operations small variabilities in media and feed component concentrations and residual impurities (e.g., trace metals or organic compounds) may lead to shifts in cell culture performance and product quality across the duration of one continuous manufacturing batch (i.e., intra-batch variability).
APIC	128	132	3.1.3	This sentence implies that the industry or drug manufacturing understanding and knowledge of their cell culture is not considered: "For a therapeutic protein (e.g., monoclonal antibodies) process, the higher variability of cell culture performance. Prolonged run times may require different lots of media, buffers, or other starting materials for the downstream CM process, potentially introducing more variabilities to the process." I have proposed an update to the text.	Please update text as follows: "For a therapeutic protein (e.g. monoclonal antibodies) process, cell culture media and feed components should be characterized and understood regarding potential impact to cell culture performance. Requirements for raw material lot consistency, including cell culture media/feed, buffers, and other starting materials for the downstream CM process, should be adjusted based on prolonged run times of CM, as necessary."
BioPhorum	137	140		Integrated flow reflects the fact that not all process operations will have a constant flow, between two or more operations the situation that not all processes are continuous end to end. Filter changes are not necessary a disruption to CM operations, because of switch valves and automated systems	These include the system’s ability to maintain an integrated flow of input and output materials between two or more operations, manage potential disruption to CM operations, and complete the intended transformation of the material stream within the respective planned operational ranges of the equipment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	137	140		The addition reflects the situation that not all processes are continuous end to end	These include the system's ability to maintain an **integrated f**low of input and output materials **between two or more operations, ...**
APIC	137	140	3.1.4	Please update the text, since filter changes are not necessary a disruption to CM operations, because of switch valves and automated systems. "These include the system's ability to maintain a continuous flow of input and output materials, manage potential disruption to CM operations (e.g., filter changes), and complete the intended transformation of the material stream within the respective planned operational ranges of the equipment."	Please update the text as follows: "These include the system's ability to maintain a continuous flow of input and output materials, manage potential disruption to CM operations, and complete the intended transformation of the material stream within the respective planned operational ranges of the equipment."
International Society for Pharmaceutical Engineering (ISPE)	145	145	3.1.4	Equipment and plant design for CM needs to consider servicing and maintenance over lifecycle (not only operational considerations).	spatial arrangement of equipment to facilitate **servicing, maintenance**, material flow …
International Society for Pharmaceutical Engineering (ISPE)	148	149	3.1.4	Prolonged differences in upstream and downstream mass flow rates are not sustainable, surge or no surge. Surge tanks are added to increase time constants which help level off fluctuations of not only extensive variables (flow rates) but also intensive ones (e.g., T, pH or composition).	e.g., use of a surge tank between two unit operations to mitigate **temporary** differences in mass flow rates and dampen fluctuations .
BioPhorum	153	153			Add - **IT control systems need to be able to monitor a process step but also link to the upstram and downstream steps, as well as the overall control / release strategy for the end product** **- In-silico models whilst being able to predict the outcome of a process step, should also be able to feedback to the system and change process parameters to bring output material back witning- acceptable ranges**
BioPhorum	162	164		The paragraph only describes the steady state	Add **Process monitoring and controls also support the assessment of the process dynamics, for example transition of materials between operations. Finally process monitoring and controls can also be used to maintain the process within set limits when feedback loops are used.**
Gilead Sciences	166	166	3.1.5	ICH Q8 defines PAT as: A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.	Does mass flow controller a PAT?
EFPIA	168	169	3.1.5	Actual implementation of in-line particle size analysis has not been observed for a CM GMP process at least in a broad sense. Suggest using a more well known and established PAT technology which is more consistent with industrial experience for the drug substance processing example. Rationale in column "Proposed changes / reccomendation"	**. . . , in-line near-infrared spectroscopy to assess blend uniformity, and ~~in-line particle size analysis to monitor the output of a crystallizer~~ on-line HPLC to monitor conversion of a chemical reaction.**
International Society for Pharmaceutical Engineering (ISPE)	168	168	3.1.5	In-line particle size analysis is not a good choice of example because it is difficult to validate and no known published commercial examples exist.	in-line UV flow cell or on-line HPLC for concentration in a drug substance process.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	174	179	3.1	Sentence is very long and complex using many brackets - very difficult to read and understand Simplification of sentence would support easier understanding	**The variables monitored, monitoring method and frequency, amount of material sampled (either physical sampling or data sampling using in-line measurement), sampling location, statistical method, and acceptance criteria depend on the intended use of the data and process dynamics. The intended use of data may include detection of rapid changes such as disturbances, assessment of quality of a batch when real-time release testing (RTRT) (ICH Q8) is used or analysis of process trends or drifts.**
EFPIA	179	180	3.1	A quite relevant consideration for the sampling approach - its impact on the material stream and the state of control Each sample physically withdrawn from the CM process reduces the material stream in the line. Hence, extensive sampling does create disturbances in the material flow and hence might affect state of control. Logically, the impact of the sampling itself on the CM material stream needs to be considered. This might not be relevant when physical sampling is done from surge tanks or buffer systems.	**Further important considerations are the avoidance of measurement interference with the process as well as the impact of physical sampling on the material stream potentially affecting state of control.**
EFPIA	184	186	3.1.6	Sentence implies that all CM processes have startup or shutdown transition waste, which has not been the industrial experience with continuous unit operations, such as CSTRs, mixer/settler extractors, evaporators, crystallizers and filters, and some drug product CM operations. This statement should not leave the impression that material must be diverted unecessarily, when the unit operations have demonstrated lack of transition waste. Rationale in column "Proposed changes / reccomendation"	**CM processes may include periods when non-conforming materials are produced, for example, during system start-up and shutdown for some CM unit operations, and when disturbances are not appropriately managed and mitigated.**
International Society for Pharmaceutical Engineering (ISPE)	184	184	3.1.6	As written, this sentence seems to imply that all CM processes have start-up or shutdown transition waste, but that is not the case for most DS continuous unit operations, like CSTR (continuous stirred tank reactors) s, mixer/settler extractors, evaporators, crystallizers, filters where relatively large amounts of non-conforming material can be dampened out.	CM processes may include periods when non-conforming materials are produced, for example, during system start-up and shutdown and when disturbances are not appropriately managed and mitigated. **Based on the downstream impact of the disturbance, material diversion may be necessary to assure product quality.**
BioPhorum	189	189			Add **The ability of trending or predicting output material quality, from in-silico models for example, and bringing back the output material to acceptable ranges and steady state also need to be considered when developing the process control strategy.**
International Society for Pharmaceutical Engineering (ISPE)	198	198	3.1.6	The use of 'downstream' emphasizes what is meant by the statement, helping clarify it.	... the diversion strategy accounts for the downstream impact on material flow and process dynamics ...
Gilead Sciences	201	239	3.1.7	Process models in the draft sometime seem being referred to QbyD/DoE type of statistic model (by JMP, Design Expert, etc.), sometime being referred to advanced/ process simulation (by Aspen, gPROMS etc.).	Suggest distinguishing the two different types of models if possible.
Regeneron Pharmaceuticals, Inc.	201	201	3.1.7	**Referenced Line Excerpt:** "***3.1.7. Process models***" **Regeneron Comment:** Use of the term "Process Models" as a header for this section could lead to confusion because it is too general. In the context presented here, we interpret the discussion under Section 3.1.7 to be more specific to in silico models of the manufacturing process, particularly in light of the reference to in silico experimentation within line 207. As such, we recommend a revision to the title to "In Silico Process Models" and that the term be added to and defined in the Glossary (Section 5). These adjustments will add clarity and likely minimize divergent interpretations that could be caused by use of the general term "Process Models."	**3.1.7. *In Silico* Process Models**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	207	208	3.1.7	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 simulations) does not add much to the sentence, thus an alternative wording is recommended.	**Proposed wording: "~~Through use of in silico exprimentation,~~ Pprocess models can ~~also~~ enhance process understanding and ~~can~~ reduce the number of experimental studies."**
BioPhorum	214	215			A process model is specific to the system design, configuration, connection between unit operations, ranges of operation, and input material properties to the system and feeds
International Society for Pharmaceutical Engineering (ISPE)	217	218	3.1.7	This sentence would benefit from a more realistic example in the parentheses; plug flow and mixed flow/CSTR are theoretical systems.	Model development requires an understanding of the underlying model assumptions **(e.g., amount of axial dispersion**) and when these assumptions remain valid.
EFPIA	219	220	3.1.7	Editorial: "(…) 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. Rationale: Refer to column "Proposed changes / reccomendation"	**Consider replacing with "and relevant data are needed to select model inputs and model formulation."** **For EWG Comment**
BioPhorum	222	222		https://www.biophorum.com/download/regulatory-feedback-to-dmka-questions-to-critical-gxp-augmented-intelligence/	Add **Model development for prediction of material output and feedback control should obey the principles described in the INDUSTRY FEEDBACK ON DMKA QUESTIONS TO CRITICAL GXP AUGMENTED INTELLIGENCE – MACHINE LEARNING APPLICATIONS for the training, validation (optimization) and testing of the models**
International Society for Pharmaceutical Engineering (ISPE)	223	239	3.1.7	Not all models need to have their performance monitored (e.g., models used for development or process optimization purposes)	"Monitoring of model performance **for a model that is used as part of the control strategy** should occur on a routine ongoing basis….
BioPhorum	232	232			Add **Model validation may be performed in the traditional way, i.e. on three consecutive batches, or in a way that reflects CM, i.e. on one batch for which variability is designed in (for example variation of input material or process parameters). In any case, model validation should be performed in conditions representative of the intended commercial process, for example shortest and longest anticipated run times.**
BioPhorum	233	234			Monitoring of model performance should **be built in the algorithm as well as** occur on a routine basis
EFPIA	252	254	3.2	Statement does not necessarily hold true for dynamic perfusion. Running shorter than the validated can impact on product quality.	**Decreasing production output (below the longest run time previously validated, but above the minimum demonstrated run time) should …**
Gilead Sciences	263	269	3.2	Is "parallel unit operations on the same production line" a true scale-out?	Suggest simplifying the wording as "increase output through scale-out (and put scale-out definition in the glossary)". Keep the paragraph "parallel unit operations on the same production line…" as a special case and require additional attention to be implemented.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	277	277	3.2	To be consistent with the headings of the previous 3 items.	· Increase output through increasing equipment size/capacity (i.e., scale-up):
BioPhorum	279	279		CQAs should be the basis of scale up - they need to remain the same	General principles of equipment scale-up as in the case of batch manufacturing apply, **especially with regards to maintenance of the control strategy** . W**hen elements such as RTD, process dynamics and system integration may change, it should be intended that the control strategy does not change. Process parameters may need to be assessed at each scale and modified where needed, but the output of each process step should be controlled to the same manufacturing intermediate end point.**
EFPIA	283	292	3.2	Check terminology on CPV, either Continued Process Verification (which is industry standard) or continous process verification (definitaion should be added in glossary if this intended to be used) To avoid confusion.	**Add to glossary**
EFPIA	284	292	3.3	Parametric controls are an additional, more common source of data for process monitoring. Propose adding it as an example. Rationale column "Proposed changes / reccomendation"	**In CM, frequent process monitoring and control can be achieved through use of <u>parametric evaluation</u>, PAT tools such as in-line/online/at-line monitoring and control, soft sensors, and models.**
BioPhorum	285	285		In addition, industry is looking for more guidance with regards to regulatory expectations. The convertion of existing batch processes to continuous processes: is there an expectation that industry will be required to correlate in-line,and off-line testing? Add the requirement for demonstration that we get the same CQAs, bridging work is needed - level of detection (aggregates are detected with the same sensitivity)	Add **for the direct measure or modelling of process parameters and attributes, whether critical or not. For example in the manufacture of a therapeutic protein, PAT monitoring may be used for the measure of pH or conductivity of the broth, for the measure of temperature, pressure, flow rate as well as the prediction of typical critical quality attributes and end points such as enzyme activity or redox activity.**
EFPIA	285	285	3.3	Editorial: ".. soft sensors and models". In the Glossary, a soft sensor is defined as a model; use of "soft sensors and models" appears redundant.	Consider adding "**...soft sensors and <u>process</u> models"**.
Gilead Sciences	285		3.3	Definition of in-line/on-line/at-line helps.	Suggest including them in the glossary
International Society for Pharmaceutical Engineering (ISPE)	286	286	3.3	To improve the statement accuracy and readability.	parameters relevant to process dynamics and **<u>output</u>** material quality
EFPIA	287	289	3.3	Development knowledge does not have to be generated at commercial scale to provide sufficient understanding and ability to use a CPV. Current language can provide the impression CPV is not possible in cases where development utilizes a different, but representative, scale. Rationale: Refer to column "Proposed changes / reccomendation"	**Additionally, since CM can facilitate changes to production output without increasing equiment size, there is an opportunity to generate development knowledge at the same scale <u>as or a scale representative of</u> ~~intended for~~ commercial manufacturing.**
International Society for Pharmaceutical Engineering (ISPE)	287	289	3.3	This sentence is problematic, because: (1) Continuous process verification is not dependent upon development being done at the same scale as commercial manufacturing (2) It implies an expectation that CM development be done at the same scale as commercial manufacturing, which is not realistic in all cases, such as small molecule drug substance CM which typically is 100-1000x smaller scale than commercial manufacturing	Delete sentence ~~"Additionally, since CM can facilitate changes to production output without increasing equipment size, there is an opportunity to generate development knowledge at the same scale intended for commercial manufacturing"~~

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	289	292		Please note that more guidance or clarification of expectations should be given with regards to the conversion of existing batch processes to continuous processes. Often different methods using different principles will be used for in-line and off-line monitoring. This also means that the methods are likely to have different limits of detection, sensitivities and accpetance criteria. Will there be a regulatory expectation for bridging studies, demonstration of equivalency? Or will the demonstration of the acceptability of the new methods for their purpose be acceptable? This is currently not addressed in the guidance but is of major concern to the industry when it comes to implementation. As this comment is made in the continuous process verification section of the document, what would be the principles for being able to use existing knoweldge of product and process understanding and impact on quality? Would that be acceptable to agencies when justified? Or would the product made according to the new process be considered as a separate entity?	
International Society for Pharmaceutical Engineering (ISPE)	292	292	3.3	The use of 'traditional' may seem reasonable in English-speaking countries but is not accepted as scientific in many other cultures.	to ~~traditional~~ process validation.
EFPIA	295	296	4.1	In line with ICH M4Q, a sequential narrative description of the manufacturing process should be included in sections 3.2.S.2.2 and 3.2.P.3.2 of the Common Technical Document (CTD) and supported by pharmaceutical development data provided in CTD sections 3.2.S.2.6 or 3.2.P.2.3.' Please advise how to capture the RTRT results: a) As IPC or release test b) As a part of bioprocess Rationale: Refer to column "Proposed changes / reccomendation" **Clarity on location of PAT and RTRT information in CTD would be appreciated.** **This comment recieved from multiple Efpia member companies**	**Please advise how to capture the RTRT results.** **For EWG Discussion**
EFPIA	296	296	4.1	**3.2.P.3.2 - to be corrected to 3.2.P.3.3** **Comment Recieved from mulitiple Efpia member companies**	**3.2.P.3.2 - to be corrected to 3.2.P.3.3**
EFPIA	300	303	4.1	As written, section may imply all operating conditions are required to be described in commitment Sections 3.2.S.2.2 and 3.2.P.3.3, as opposed to those adequate to describe the process. Operational strategy may have different interpretations, and may encompass GMP aspects which are not provided in Section 3.2.S.2.2 and 3.2.P.3.3, which focus on the control strategy. Propose simplification to focus on key control strategy elements. As the manufacturing processes may be either described by operating ranges or multivariate design spaces, we recommend removing the examples in paranthesis as they do not involve complex design space options. Proposal with all changes is provided.	**An adequate description of the CM process ~~operations strategy~~ indicating the operating conditions ~~(e.g. such as mass flow rates, setpoints, ranges)~~, in-process controls or tests, criteria that should be met …**
International Society for Pharmaceutical Engineering (ISPE)	300	301	4.1	Phraseology should be consistent with CTD and Table 1, line 480 ff. "Operational Strategy" is not defined and not a well understood phrase. Set points are not necessarily included in the process description as these sometimes can be varied (e.g., within approved ranges or design space)	**A description of the CM process and** ~~operational strategy~~ indicating the operation conditions (e.g., mass flow rates, ~~setpoints,~~ ranges)
BioPhorum	304	304		This aspect is missing from the guidelines, however a clear plan and strategy needs to be part of the process description to minimize material waste and shortage	Add **A description of the strategy for material being diverted from the main process should be defined - for example, quarantined material that requires further assessment prior to potentially be accepted as part of the main batch (conditions and acceptance criteria), quarantined material that is acceptable for rework prior to potentially be accepted as part of the main batch (conditions, description of the rework process and acceptance criteria), description of material that must disposed of (conditions and acceptance criteria).**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	305	305		Missing from the current text but important	Add **The physical state of the material (solid, free flowing powder, liquid etc) may need to be described so that the adequacy of the transfer method can be assessed.**
BioPhorum	305	305		Missing from the current text but important	Add **Description of material transfer should include whether this is done in a continuous mode or whether holding tanks or break bags are required.**
Gilead Sciences	305		4.1	A description of how the material is transported from one piece of equipment to another (e.g., vertical, horizontal or pneumatic conveying system).	Is this more applicable to DP? Suggest specifying for DP or remove. The transportation of material can be quite flexible in a DS facility, for the setup and the method. Including information like this will introduce unnecessary regulatory burden for DS sites.
International Society for Pharmaceutical Engineering (ISPE)	305	306	4.1	Transfer of materials between unit operations should be considered a GMP aspect (as in traditional batch manufacturing) and not part of the process description (i.e., an established condition) to be included in the process description	Delete sentence, ~~"When appropriate, a description of how the material is transported from one piece of equipment to another (e.g. vertical, horizontal or pneumatic conveying system)"~~
Gilead Sciences	308	320	4.1	The word "locations" is a bit confusing. It can be interpreted as a specific/exact location. But, from the example in the Annex I, the description of a flow diagram "location" is quite conceptual.	Suggest changing wording Locations to other wording.
International Society for Pharmaceutical Engineering (ISPE)	319	320	4.1	The term control is used in multiple ways in the same sentence. “Tests” is the word used in ICH Q6A and B.	… and final product quality **tests** are conducted
Gilead Sciences	322	324	4.1	This requirement seems to request to verify specific (or non-specific) equipment design features for a flow reactor system, which is beyond typical regulatory requirements and unnecessary. Industries typically only know a conceptual equipment feature works after it is realized in a plant, but it is not necessary to go through a procedure to prove that it has to be the feature--it may or may not be the feature that makes a process work the way it is. In DS filing, it is not required to explain why a specific reaction/drying/milling condition works.	Suggest deleting "A suitably detailed description of any aspects of equipment design or configuration and system integration that were shown during development to be critical to process control or to impact product quality"
International Society for Pharmaceutical Engineering (ISPE)	325	330	4.2	Section 4.2 interweaves elements of the control strategy that are in the dossier and those that are in the application in a way that is unclear. The control strategy should be thought of holistically. Including too much detail in the control strategy in a Dossier of all elements of holistic control strategy can lead to burdensome post approval changes and corresponding lack of flexibility and loss of continual improvement opportunities for CM.	It should describe the relevant controls and approaches used during manufacturing ~~and the operational aspects of~~ the CM process
APIC	325	325	4.20	Add input on recycle for reactors, and other unit-ops to increase efficiency and/or change reaction dynamics	Recycle for Chemical API synthesis reactors can utilize recycle streams to change reaction dynamics or increase efficiency of the reactor.
APIC	325	325	4.20	Add input on rework, how it integrates, can you use a single unit-op to conduct rework? Should a batch rework system be developed? is rework possible at all?	Chemical API synthesis should utilize sIngle unit-operation reworks (batch or continuous) or a small rework train should be developed to fix known issues that crop up e.g. low yield, improper fluid properties, or poor selectivity.
EFPIA	326	327	4.2	Run time language can cause confusion in cases where CM batches are defined based on a quantity. As defined in the glossary run time may include periods of acceptable and unacceptable quality. Run time reference is not needed for intended purpose of the sentence. Rationale in column "Proposed changes / reccomendation"	**The control strategy of a CM process is designed to ensure that output materials ~~made over the run time~~ are of the desired quality.**
International Society for Pharmaceutical Engineering (ISPE)	326	327	4.2	Consistent quality cannot be reliably delivered by a non-robust process. The proposed statement adds that to the existing necessary but insufficient claim on quality only.	The control strategy of a CM process is designed to ensure that output materials made over the run time are of the desired quality **and that the process remains in a state of control.**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	332	336	4.2	Although wording is listed as an example, the reference to intra batch implies there will be significantly higher risk or sensitivity to intra batch variation for CM vs. batch processes which is not necessarily true. Additional wording is suggested to emphasize the point to understand variability in materials overall with regard to impact on CQA's. Rationale in column "Proposed changes / reccomendation"	**Impact of input material attributes and their variability (e.g.,~~intra batch,~~ inter-batch, different suppliers) on continuous processing should be assessed based on potential risk to CQAs and proposed material attirbute acceptable ranges should be justified when establishing the material specification."**
BioPhorum	335	336		The added text would be a good starting point. But clarification and more details around regulatory expectations would be extremely useful, as from the team's experience, this lack of details leads to very different expectations across the different ICH members. Add the referrence to the BioPhorum paper when published.	Add **For example applying the principles of definition of Critical Material Attributes specific to a product or a family of products should be applied when possible. Prior knowledge captured in literature references may be a suitable reference**
International Society for Pharmaceutical Engineering (ISPE)	342	346	4.2	Many of the control strategy elements included in the paragraph on “Process monitoring and control” is information that is managed in the quality system and not typically included in the dossier or considered to be established conditions. These include: sampling strategy, quality related decisions, models for monitoring (such as MVSPC), and certain in-process control, and justification of the sampling plan and data analysis.	**Process monitoring and control:** ~~An appropriate description should be provided in the dossier to show a~~ **The control strategy in the dossier should include a** robust approach to monitoring and maintaining a state of control. Approaches on how the control system uses process parameters and in-process material attribute measurements to make process- and quality-related decisions (e.g., to pause the process or divert material) should be described **in site PQS documentation.** Other important aspects should be defined **in the PQS** such as the sampling strategy (e.g., location, sample size, frequency, statistical approach and criteria, and their relevance to the intended use), summary of the models if used (e.g., multivariate statistical process control), and the use of data in making in-process control decisions (e.g., to trigger material diversion). Fluctuations or variability that may occur during the CM process should not be masked by the data analysis method used. For example, when data averaging is used, averaging across appropriate time-based intervals should be considered rather than data averaging across the time for an entire CM run. Therefore, statistical sampling plans and data analysis should be ~~described~~ **documented** and justified.
International Society for Pharmaceutical Engineering (ISPE)	348	349	4.2	To improve the statement accuracy and readability.	when data averaging is used, averaging across appropriate time-based intervals (**e.g., relevant to the PAT method monitoring frequency**) should be considered rather than data averaging across the time for an entire CM run. The **time-intervals can consider the mean residence time, process response time or involved process time constants.**
Gilead Sciences	356		4.2	Fluctuations are only used once in the draft. It is not very clear the difference between fluctuations and disturbances. If fluctuations have no impact to the process, then the action of “masked by the data analysis method used” should not be an issue. If it is a “large” fluctuation, which then should be disturbance.	Either define fluctuation or choose other word/phrase.
International Society for Pharmaceutical Engineering (ISPE)	359	360	4.2	The details of the material diversion material should be maintained in the PQS. The current text implies submissions in the dossier.	The material diversion and collection strategy should be ~~described~~ **documented** and justified.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	369	369			Add - P**rocedures for recycling and rework should also be in place. For example, recycle for Chemical API synthesis reactors can utilize recycle streams to change reaction dynamics or increase efficiency of the reactor and chemical API synthesis should utilize sIngle unit-operation reworks (batch or continuous) or a small rework train should be developed to fix known issues that crop up e.g. low yield, improper fluid properties, or poor selectivity.**
EuropaBio	370	370		RTRT models failing or trending toward failure does not necessarily mean product impact.	Suggest adding a line on the use of reference methods if RTRT is not working, as a possible outcome of the investigation. If RTRT is trending towards failure, there should be an investigation; if the investigation warrants it, we should be able to test by another method.
Regeneron Pharmaceuticals, Inc.	370	370	4.2	**Referenced Line Excerpt:** "***RTRT:*** *RTRT may be applied to some or all of the output material quality attributes. […]"* **Regeneron Comment:** The first reference to "real-time release testing (RTRT)" in line 178-179 is present within a larger paragraph of text. In line 370, the abbreviated term "RTRT" is used, but the meaning of this abbreviation is not readily apparent unless searching for the previous description of the RTRT abbreviation in line 178-179. We suggest updating the bullet header in line 370 to "Real-time release testing (RTRT):" as shown in the corresponding Proposed Changes/Recommendation column. This would add clarity directly to this section of the document and avoid confusion or delay in interpretation of the content within this paragraph. We also request that the Agency consider adding this term and its definition to the Glossary (Section 5) for further clarity.	**Real-time release testing (RTRT):** RTRT may be applied to some or all of the output material quality attributes. [...]
EFPIA	371	372	4.2	It may not always be true that an "associated reference test method" exists for RTRT; text seems to imply it is required Revise to remove implication by saying "where applicable"	**Proposed edit: "When RTRT is proposed, the associated reference test method should be described, where applicable."** **FOR EWG COMMENT**
International Society for Pharmaceutical Engineering (ISPE)	372	375	4.2	To improve the statement accuracy and readability, making reference to LCM aspects of a PAT method when used as RTRT (under the high-criticality model risk-tiered approach).	Development of the data collection approach for RTRT implementation should include a risk-based **lifecycle management plan for maintaining that procedure and dealing with events that may affect decisions relating to product quality** (e.g., recalibrating a near infrared (NIR) probe or lapses in data collection).
APIC	382	384	4.2	Details should be given on what level of the information should be attached here. Only basic information on the equipment and "operational principles" or details as the name of the manufacturer of the equipment... What is the regulatory relevant change in the equipment that API/FDF manufacturer should report to relevant HA?	
BioPhorum	389	389		The title should flag out to the reader the presense of "Size Aspects" discussed in the section	Batch Description and Size Aspects
EFPIA	389	389	4.3. Batch Description	The title should flag out to the reader the presense of "Size Aspects" discussed in the section . Rationale: of note, the section at present repeatedly cites "Size". The title should be more complete.	The revised and more complete title should be: **"4.3. Batch description and size aspects" OR "Batch Size"**
APIC	389	389	4.3	The title should flag out to the reader the presense of "Size Aspects" discussed in the section . Rationale: of note, the section at present repeatedly cites "Size". The title should be more complete.	The revised and more complete title should be: "4.3. Batch description and size aspects"

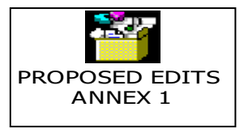
Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	390	405	4.3	The definition of batch / lot size should be clarified and has to be in line with the definition on line 487-491. It should be evident in the main text that a batch/lot can be a fraction of the production. A continuous process can run over several weeks and it is important from a practical and operational perspective that lots can be generated, released and taken into further processing (for example packaging) while the "main process" is still running.	**Introduce the notion of production run and that a batch / lot can be a defined fraction of the production run (in accordance with the definition)** **SEE GLOSSARY DEFINITION -- SUGGEST LINE 60**
International Society for Pharmaceutical Engineering (ISPE)	395	397	4.3	The original statement is problematic because (1) there may be no “approved range” for production output, based on the product type and application 2) there may be no reporting requirements for change in production output 3) changes within an “approved range” may still require validation activities, depending upon the risk of the change 4) Section 3.2 does not include data requirements; unclear why referenced	Any post-approval change to the production output beyond the approved range should be supported by data ~~(Section 3.2)~~ ~~and appropriately managed (i.e., prior approval or notification)~~ **using risk based considerations.**
International Society for Pharmaceutical Engineering (ISPE)	399	400	4.3	The metric for consistency and robustness should described as a quality system parameter	A suitable quantitative metric should be defined **within the PQS** to establish batch-batch consistency and system robustness.
International Society for Pharmaceutical Engineering (ISPE)	401	401	4.3	As diversion can be extended for precautionary reasons, using a metric based on the ratio of diverted materials to overall output as metric would penalize those using such conservative estimation of robustness. Why establish a link between batch size and quality robustness? CM was proposed to allow manufacturing flexibility (as quantities produced) at equal or higher quality consistency levels.	**Change "should" to "could"**
EFPIA	408	408	4.1 Table 1	It could help if the CTD dossier table could include more details Rationale in Column "Proposed changes / reccomendation"	More details like the ones included in the Quality Considerations for Continuous Manufacturing (Section IV location of information in an application – Page 19 to 21) guidance issued by FDA.
EFPIA	409	411	4.4	It may be unnecessarily inflexible to require all information for models to be maintained at the commercial manufacturing site. It may not be appropriate for a CMO to hold all the model information for a model developed by the license holding company. Or a company may maintain the model information centrally for a model used at multiple manufacturing sites.	Delete the sentence on lines 409-411 beginning with "All information", or otherwise edit to allow for scenarios where all or part of the model information would be maintained at another site other than the manufacturing site.
Gilead Sciences	409	411	4.4	"All information for models used as part of commercial manufacturing should be maintained at the manufacturing site". "All information" is too broad. Could it be more specific (e.g. model development, validation and maintainence)? Please also clarify what "maintained at the manufcaturing site" means.	
BioPhorum	414	420		Industry would be very gratful if the guideline could be clearer on the regulatory expectations with regard to what constitutes a pilot batch for continuous manufacturing. The current wording is too vague for a clear direction when it will come to implementation.	
BioPhorum	414	420		For batch manufacture, it is not unusual for industry to use development batches manufactured on different manufacturing equipment and in different facilities than those intended for commercial manufacture. A risk-based approach may be used to justify the accpetability of these supporting data, especially when the differences have no impact on stability. It would be expected that the same approach is also acceptable for continuous manufacturing batches; however the current wording of the guideline does not really allow for such an approach	
EFPIA	415	418	4.5	**CRTIICAL**: ICH13 should give clear support to the industry on which manufacturing approach is accetable for (primary) stability sample manufacture. It is scientifically sound to assume that the length of the manufacturing run will have no impact on product stability, provided samples are within (release) specification at the time of manufacture. Rationale: Refer to column "Proposed changes / reccomendation"	Replace sentence lines 417-418 with (wording may be improved): **"Instead, A key criteria is that samples for stability testing are been taken when the system is in the state of control". EWG TO COMMENT ON CRITICALITY**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	415	417	4.5	"The concept of using a pilot scale batch for stability studies, as defined in other guidelines (e.g. Q1A), may not be applicable to CM". The paragraph below provided additional clarifications and examples that batches with shorter run time from commercial equipment and process can be used for stability. Can we assume that the "pilot scale batch" means the batches manufactured using pilot equipment e.g. smaller scale equipment? More clarity on definition of "pilot scale batch" would be helpful.	
EFPIA	417	418	4.5	**CRITICA**L: Remove sentence: "See Section 3.2 for considerations that should be taken into account if production output between stability and commercial batches is different". 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. Reference to section 3.2 does not add value as DS/DP stability is not mentioned in section 3.2. The general comment to see section 3.2 for details on scale up procedures is not adding value at this part of the text. Suggestion to remove this sentence recieved from multiple Efpia member companies	Remove sentence. **EWG TO COMMENT ON CRITICALITY**
International Society for Pharmaceutical Engineering (ISPE)	417	418	4.5	There is no information on Section 3.2 that can support the claim that stability was addressed there.	Remove sentence starting "See section 3.2 for…"
EFPIA	420	421	4.5	How about stability data generated from clinical batches mainly phase 3. Could the manufacturer consider them as additionnal primary stability data to support the shelf life ? Rationale in Column "Proposed changes / reccomendation"	**Please consider use of supplemental stablity data, e.g. From late phase clinical supply to satisfy stability requiements for CM processes to enable flexibility in bridging primary stablity to subsequent commerical mfg process.**
International Society for Pharmaceutical Engineering (ISPE)	423	425	4.5	To improve the statement accuracy and readability.	Multiple stability batches may be produced from shorter manufacturing runs at the same mass flow rate, provided it is demonstrated that a state of control is established **across all these runs**, **that is representative of the commercial run times.**
International Society for Pharmaceutical Engineering (ISPE)	426	426		To improve clarity.	Alternatively, for chemically **derived drug substances or drug products,**
International Society for Pharmaceutical Engineering (ISPE)	429	440	4.5	Please address the simultaneous inclusion of both batch and continuous process in the same dossier. This approach is consistent with ICH Q8/9/10 Points to Consider Document Section 3 which provides that "Different control strategies could be applied at different sites or when using different technologies for the same product at the same site". This inclusion is critical for manufacturers who want to gain experience with CM before fully committing to using it as a sole approach.	**It may be possible to have control strategies for both batch and continuous manufacturing in the same dossier. In such cases, the appearance and performance of the product need to be the same between the two processes.**
APIC	429	429	4.6	Is it possible to describe in the one DMF for the same API both batch manufacturing process and continuous manufacturing process, if both give the same quality of the API?	
EFPIA	430	440	4.6	Not enough detail. Mainly, include the data to be generated to support the coversion of mode batch manufacturing system to a continuous manufacturing Rationale: Refer to column "Proposed changes / reccomendation"	Include the data to be generated to support the coversion of mode batch manufacturing system to a continuous manufacturing **FOR EWG DISCUSSION**
International Society for Pharmaceutical Engineering (ISPE)	430	431	4.6	There are several elements that may be re-usable when migrating a batch to continuous process.	Changing the manufacturing mode from batch to continuous necessitates the development **(or re-development)** of an appropriate control strategy,
APIC	432	433	4.6	In case CM is applied only to the DS, is the science and risk-based approach also expected to be available for DP (that can be manufactured batch wise)? Or the proof of equivalence would be sufficient on the DS level as well?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	433	434	4.6	It is proposed to clarify when additional BE study should be done - in the case of the conversion of the batch process to continuous process. In the case that conversion of the batch process to continuous process does not impact the quality of the API, the request for re-do of the BE study is too strict and unnecessary.	
EuropaBio	436	436		Suggested to seek advice before converting batch to CM process. What about CM to batch? Is there any reason to think that this would be different or less accepted to switch from CM to batch?	Regulatory approval should not be needed; consultation may be helpful, but approval would be at the time of the submission. Suggest to remove line 436
International Society for Pharmaceutical Engineering (ISPE)	437	438	4.6	Recommend deletion. Not all changes of manufacturing process may require regulatory approval (e.g., monographed OTC products within US).	~~Manufacturers should seek regulatory approval before the conversion of an approved batch process to a CM process~~.
EFPIA	440	440	4.6	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. Rationale: Refer to column "Proposed changes / reccomendation"	Add the following setence 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."** **Comment and criticality for EWG discussion.**
International Society for Pharmaceutical Engineering (ISPE)	443	443	4.7	The use of 'traditional' may seem reasonable in English-speaking countries but is not accepted as scientific in many other cultures.	to ~~traditional~~ process validation
EFPIA	448	449	4.7	As written, it would appear that continuous process verification would require continuous monitoring. It is unclear how this sentence would apply to a CM process which has some batch unit operations. Rationale: Refer to column "Proposed changes / reccomendation"	**Remove the word continously**
International Society for Pharmaceutical Engineering (ISPE)	448	448	4.7	clarification	When continuous process verification is used, the CM system performance and **output** material quality
International Society for Pharmaceutical Engineering (ISPE)	449	449	4.7	This is the essence of CPV and not solely a regulatory requirement	Change "should be monitored" to "is continuously monitored"
International Society for Pharmaceutical Engineering (ISPE)	451	452	4.7	The CPV program is an 'end-of-pipe' confirmation that the CQAs in the output material match those intended by the control strategy – and not the reverse.	The dossier should contain justifications about the **capability** of the continuous process verification procedure to assure the proposed control strategy.
BioPhorum	454	456		Current wording is vague. Applicants would be happy to propose the number of batches that they consider sufficient. This will be based on statistical approaches and accptance criteria that they would have set. The actual number of batches will therefore depend on process capability. It is the BioPhorum's team experience however that the actual expectations from the different ICH members are different, and not all accept this approach. It would therefore be our recommendations that the regulatory expectations are defined in a more concise manner.	
APIC	469	469	4.9	Will same criteria as provided in relevant guidelines for Post-approval changes be applicable for DS and DP manufactured under CM (especially those connected to manufacturing process – e.g. change in batch size, equipment change)?	
International Society for Pharmaceutical Engineering (ISPE)	471	472	4.9	There is no information on Section 4.6 that can support the claim that LCM aspects was addressed there.	Delete sentence " Additional lifecycle management aspects related to conversion of a batch to a CM process for existing products can be found in Section 4.6."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	480	480	Table 1	Propose moving operational strategy elements, that should be managed within the PQS, from the manufacturing process sections (3.2.S.2.2 and 3.2.P.3.3) to the process development sections (3.2.S.2.6 and 3.2.P.2.3). Assurance of product quality is not only managed by the manufacturing process, but also by the specification. The strategy for segregation or diversion may change over the lifecycle and may be appropriately managed within the PQS, as long as the manufacturing operating conditions committments and specification are maintained. Additionally specific control limits may vary with process performance over the life cycle of the product and are best managed within PQS. Refer to column "Proposed changes / reccomendation"	**Description of Manufacturing Process and Process Controls** **• Commercial manufacturing process description, including flow diagram and equipment scheme** **• Process controls ~~and limits~~ (e.g., input rates/mass flow rates~~, feeder control limits~~)** **• Critical process parameters** **• Active controls (e.g., feedforward or feedback control) and process models, if these elements are part of the control strategy** **• Criteria for product collection~~, including control limits and strategy for segregation and diversion to waste~~** **• Description of equipment and system integration critical to the output material quality** **• Overview of high-impact process models, if used** **Also move the phrase "Strategy for segrgreation and diversion to waste" to Section 3.2.S.2.6 / 3.2P.2.3 in Table 1.**
EFPIA	480	480	4.10	Table 1, CTD Sections 3.2.S.4.5 and 3.2.P.5.6: The item "Justification of the overall control strategy" seems out of place in these sections; would perhaps fit better in S.2.6. Certainly, the description of these sections in M4Q would not require this information to be included here. Furthermore, this feels like something that would be handled similar to batch processing, not something unique or special to CM. Analytical controls; Analytical Control Strategy: If defined in another guidance, please use this definition. This comment was recieved from more than one Efpia member company	**Consider providing more detail or definition for analytical control strategy.**
EFPIA	480	480	Table 1	Per ICH M4Q, 3.2.S.4.5. and 3.2.P.5.6 should contain content related to the drug substance or drug product specifications. Propose clarification in the Justification of Specification sections of Table 1 that the PAT described here only relate to those that are used for RTRT/release decisions of drug substance or drug product since PAT that is only used for in-process control and not for RTRT should not impact specifications, and thus should not relate to sections 3.2.S.4.5 and 3.2.P.5.6. Refer to column "Proposed changes / reccomendation"	**Summary of the analytical control strategy (including alternative plans instituted when potential gaps in ~~PAT~~ RTRT data occur, where relevant)**
EFPIA	480	480	Table 1	3.2.S.2.4/3.2.P.3.4 Controls of Critical Steps and Intermediates The summary of in-process testing or control and the acceptance criteria that will assure state of control are important elements in this section. On the other hand, we propose that the sampling plan move to section 3.2.S.2.6/3.2.P.2.3 to allow the ability to adapt to information learned over the lifecycle of the drug. This is better managed in the PQS to facilitate appropriate and efficient updates based on that learning. Alternatively, for chemical entities, a single CM run with a single start-up/shutdown sequence	**~~Controls of Critical Steps and Intermediates~~** **• Summary of in-process testing or control and acceptance criteria** **• ~~Sampling plan for in-process testing or control~~** **• High-impact process model validation data and maintenance protocol, if used.** **Move Sampling plan for in-process testing or control to 3.2.S.2.6/3.2.P.2.3**
Gilead Sciences	480	480	4.1	CTD section 3.2.S.2.4 and 3.2.P.3.4, "Summary of in-process testing or control and acceptance criteria" is common for both batch and CM processes. Are there any specific requirements for CM? Otherwise, it may be removed.	
International Society for Pharmaceutical Engineering (ISPE)	480	480	4.9	eCTD 3.2.S.2.2 row: clarification	· Summary of disturbance management **to maintain a state of control**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	480	480	4.9	eCTD 3.2.S.2.2 row: (1) It is beyond current expectations to include all process models as part of the manufacturing description. For example, every modern tablet press has embedded process models that are not described in applications for traditional tablet manufacturing (2)Control limits for product collection are a part of GMPs and not the dossier; they may change with experience	Active controls (e.g., feedforward of feedback control), ~~and process models~~ if these elements are part of the control strategy Criteria for product collection, including control limits and strategy for segregation and diversion to waste"
International Society for Pharmaceutical Engineering (ISPE)	480	480	4.9	eCTD 3.2.S.2.4 row: Sampling plans for in-process testing or control should be managed within the quality system and not be an established condition	Summary of in-process testing or control and acceptance criteria ~~Sampling plan for in-process testing or control~~
International Society for Pharmaceutical Engineering (ISPE)	480	480	4.9	cCTD 3.2.S.4.1/4.2 row Request clarification on what criteria are needed for RTRT or delete "and criteria". Note that acceptance criteria is part of the RTRT procedure and does not need to be separately detailed ~~ Without additional language unclear what the expectations are for documentation.~~	· Description of the RTRT methods ~~and criteria~~ where used for release
APIC	480	480	4.10	Applicable to 3.2.S.4.1/4.2 // 3.2.P.5.1/5.2 and 3.2.S.4.5 // 3.2.P.5.6 rows: In case DS is produced through hybrid process (combination of CM and batch manufacturing) is it expected that also some points of CM control strategy (such as in-process controls) to be included in DS specification? Is description of RTRT methods expected to only be included for DS/DP fully manufactured in CM mode in addition to conventional testing methods?	
EFPIA	486	512	5	Add definitions for in-line/online/at-line monitoring to Glossary Provide clarity on the meaning of these terms. Proposed definitions are from BioPhorum white paper "In-line monitoring / real-time release testing in biopharmaceutical processes - prioritization and cost benefit analysis" (2020): https://www.biophorum.com/download/in-line-monitoring-real-time-release-testing-in-biopharmaceutical-processes-prioritization-and-cost-benefit-analysis/	"**At-line:** The sample is removed, isolated from, and analyzed in close proximity to the process stream." "**In-line:** The sample is not removed from the process stream. The measurements can be invasive or non-invasive" "**On-line:** The sample is diverted from the manufacturing process, and can in some cases be returned to the process stream if desired"
BioPhorum	487	491		Our comment would be in line with that on lines 51 - 64, a batch size may be defined by many other criteria. This definition should align with this concept.	
EFPIA	501	501	5	Define "high-impact model" in Glossary High-impact model used in Table	"**High-Impact Models:** A model can be considered high-impact if prediction from the model is a significant indicator of quality of the product (e.g., a chemometric model for product assay, a surrogate model for dissolution)."
Gilead Sciences	503		5	Not clear if the wording of "distribution of material" refers to the distribution of a batch of material in the product vs. diversion, or a real time distribution of material inside a flow system etc.	Refine wording.
International Society for Pharmaceutical Engineering (ISPE)	503	503	5	The proposed writing attempts to be more accurate in what is being traced / tracked.	The ability to track defined components of the material flow throughout a CM process.
EFPIA	511	511	5	Incorrect abbreviation for European Pharmacopoeia This comment recieved from multiple Efpia member Companies	**Change EP to Ph. Eur.**
EFPIA	512	512	5	Add "Process Analytical Technology (PAT)" to Glossary Provide ICH definition of terminology (and abbreviation) used frequently in the guideline	"**Process Analytical Technology (PAT):** A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. (ICH Q8)"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	515	515	5	Add "Real Time Release Testing: (RTRT)" to Glossary. Provide ICH definition of terminology (and abbreviation) used frequently in the guideline.	"**Real Time Release Testing: (RTRT):** The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. (ICH Q8)"
EFPIA	521	522	5	Propose to add glossary for "state of control" as well. "state of control" is a very important characteristic term for CM - should be listed in glossary. "State of control" is defined in the text in section 3.1.1 - so propose to include it in section 5 as well	**State of control (ICH Q10) is a condition that provides assurance of continued process performance and product quality. The condition may vary, depending on the mode of CM and the specific process steps.**
International Society for Pharmaceutical Engineering (ISPE)	534	534	5	typo	equipment, their connections to one another**,** monitoring and control systems, and
International Society for Pharmaceutical Engineering (ISPE)	543	545	5	Changed to include biological DS processes (cf. Annex III). The list was also sorted to have 3 examples for each of the 3 types given.	A basic step in a process. Unit operations involve a physical, chemical or **biological** transformation such as: reaction, crystallisation, filtration, blending, granulation, tableting, **cultivation,** purification or virus inactivation.
BioPhorum	588	589		This is the language used for other ICH annexes, specifically ICH Q12. Please align.	The discussion points presented here for drug substance CM systems are mock examples provided for illustrative purposes.
EFPIA	588	589	Annex I, Section 1	This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The discussion points presented here are not exhaustive for drug substance CM systems."	Change please to: **"The discussion points presented here for drug substance CM systems are examples provided for illustrative purposes." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)**
APIC	588	589	Annex I, 1	This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The discussion points presented here are not exhaustive for drug substance CM systems."	Change please to: "The discussion points presented here for drug substance CM systems are mock examples provided for illustrative purposes. ." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)
EFPIA	592	592	Annex I, Section 1.	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?	**Provide an update to Figure 1 to represent a regulatory flow diagram to serve as an example for authors.** **For EWG Discussion**
EFPIA	598	600	Annex 1	Although the process flow in Figure 1 could be possible, upon further review there are a few elements which do not fully reflect the current thinking and more common practice for how such a system would be more likely designed. Edits are suggested to both update the figure/process description and simplify the example. These do not impact the explanation of related principles from the main guidance. A simpler process will allow additional focus on the more important aspects of the application of the guidance, rather than any questions or uncertainty on the process details. See column "Proposed changes / reccomendation"	
International Society for Pharmaceutical Engineering (ISPE)	598	598	Annex I	The process illustrated in Annex 1, Figure 1 will make more sense if there is a continuous evaporator upstream of the continuous crystallizers. Most API crystallizations also begin with a distillation step to concentrate the API before crystallization.	**Add a continuous evaporator upstream of the continuous crystallizers in Annex 1, Figure 1, and describe in the process description.**
International Society for Pharmaceutical Engineering (ISPE)	599	599	Annex I	The process illustrated in Annex 1, Figure 1 will be more realistic if there is a mixer settler with aqueous layer separation included after reaction 2 PFR, just like the one after the reaction 1 PFR. Reaction 2 PFR is a final coupling reaction between two intermediates; therefore, it will most likely have reagents and by-products that need to be washed out into an aqueous phase.	**Include a mixer settler with aqueous layer separation after reaction 2 PFR.**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	625	625	Annex I		on one filter unit at the same time product isolated on the second filter is **washed an**d discharged
International Society for Pharmaceutical Engineering (ISPE)	630	632	Annex I	Surge point 1 is after only a single reaction with quench and layer separation, and the flow is truly continuous coming out of liquid-liquid extraction at this point, therefore it should be able to flow directly into the second PFR. We typically would only put a first surge point after an intermittent flow unit operation or after a significant number of unit operations, to provide a decoupling breakpoint. In contrast, in the Annex 1 example, there is no obvious reason to justify the first surge point as shown in Figure 1 and described in the text. Surge point 3 is after filtration, which we suggest does not make sense. We suggest changing the part of the process Figure 1 after the continuous crystallizers. Dual filtration, followed by surge point 3, followed by batch filter drying does not make sense. If the first batch operation is filter drying, then slurry flowing from the continuous crystallizers would more likely either (1) flow directly onto one of two parallel filter dryers that switch back-and-forth, or (2) accumulate in a large surge vessel before any filtration, then transfer onto a large single filter dryer, or (3) accumulate in a large surge vessel before any filtration, then transfer to a centrifugal filter and dryer combination. Alternatively, the slurry emerging from the continuous crystallizers could flow into a continuous filter/dryer which continuously discharges dried solids.	We recommend removing surge points 1 and 3 to make the process more realistic. Only surge point 2 makes sense. The corresponding text should be changed. Also, please change dual filters to filter/dryers and discharge dry solids.
International Society for Pharmaceutical Engineering (ISPE)	637	639	Annex I	The PFR design does not impact reactant flows. The feed pumps or feed control valves impact reactant flows. The PFR design impacts reactant heat and mass transfer rates, and reaction time. It impacts reaction time because the orientation of the PFR and the diameters of uphill and downhill portions can impact % liquid filled.	For example, PFR design elements (i.e., dimension and configuration) allow precise control of temperature, **heat and mass transfer rates and reaction time.**
EuropaBio	645	647		Section 2.2 Process Control states that feed rate of intermediate 2 is controlled by PAT measurement of Intermediate 1. However there is no PAT measuremnt point shown in the equipment diagram that would allow measurement of Intermediate 1 unless it is a manual sample taken at surge point 1.	This could be a mistake in the equipment diagram so a PAT measurement point needs to be added or if the measurement of Intermediate 1 is taken at the surge point this should be stated in the text to avoid confusion regarding the process control strategy
International Society for Pharmaceutical Engineering (ISPE)	645	645	Annex I		with minimal impurity formation is ensured through control of the reaction temperature **and time**
EFPIA	649	649	2.2	Not clear if "process-related impurities" in the ICH Q6B sense is intended where "process impurities" is used. While the example is small molecule-specific, the terminology could still be confusing to readers mainly familiar with biopharmaceuticals. "Process-related impuriities" is the formal terminology defined in ICH Q6B as applied to biopharmaceuticals. ICH Q6A uses the term "process impurities" exactly once without defining the term ("Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit."). Confusion for the reader between the meanings of the two terms is possible.	**Change "process impurities" to "process-related impurities" unless that meaning (i.e., not product-related) is not what is intended in the sentence, or otherwise inappropriate to this small molecule example.** Another option, replace as follows: Old text: "The PAT also measures levels of crude drug substance and process impurities, which confirm successful operation of all preceding steps and consistent product quality." **Proposed new text: "The PAT also measures levels of both crude drug substance and impurities, which confirm successful operation of all preceding steps and consistent product quality."**
International Society for Pharmaceutical Engineering (ISPE)	655	656	Annex I	We suggest adding the word "some". This is an important clarification lest the guidelines inmply that experimental tracer studies will be done for all segments of the flow train. That would be a significant and unnecessary barrier to implementing DS CM.	was then confirmed through experimental tracer studies for **some** appropriate segments of the commercial equipment
International Society for Pharmaceutical Engineering (ISPE)	658	658	Annex I	"RTD" is used to mean residence time. It is not residence time.	duration of diversion informed by the **residence time and** RTD
International Society for Pharmaceutical Engineering (ISPE)	665	665	Annex I	Residence time and RTD must both be known. RTD does not mean residence time.	The criteria for diversion were established based on time considering **the residence time and** RTD.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	666	667	Annex I	It is typically not feasible to do experimental work in the commercial equipment for drug substance. It may be true for DP, but not for DS. We need to be careful that the wording does not imply that it is necessary to do experimental work in the commercial equipment. That could be a show-stopper for continuous DS because of lack of resources, and it is not necessary. Development studies can be justified for commercial equipment without repeating the development experiments in commercial equipment.	This approach was supported by development studies and **justified** for commercial process equipment.
EFPIA	673	675	Annex I	Regarding " The measurement frequency of the PAT at Reaction 2 is sufficient to detect disturbances, inform process adjustments, and ensure timely diversion..." The proposed change clarifies that the PAT system does not need to detect all disturbances in order to be a useful and important component of the overall control strategy. Low-frequency PAT systems can provide high specificity to monitor reaction conversion, detect process drift, inform process adjustments, and inform divert decisions. Thus monitoring of process parameters could have an even bigger purpose in detecting and managing disturbances compared to PAT. Rationale in column "Proposed changes / reccomendation"	**"The measurement frequency of the PAT at reaction 2 is sufficient to detect certain disturbances, inform process adjustments, and ensure timely diversion of material based on predefined criteria."**
International Society for Pharmaceutical Engineering (ISPE)	673	673	Annex II	Use “process drift” instead of “disturbances”. One of the most useful and most important types of PAT at the outlet of a continuous reactor is online HPLC because of specificity. Online HPLC will not detect all disturbances emerging from a plug flow reactor because of the frequency. It will detect process drift, but it will not detect all the disturbances. However, there are other parameters that would detect the disturbances such as mass flow rate measurements, temperatures, pressures, and these are measured in conjunction with PAT. We do not want readers to think that the PAT must detect all disturbances, because that could disqualify one the most valuable types of PAT.	The measurement frequency of the PAT at Reaction 2 is sufficient to detect **process drift,** inform process adjustments, and ensure timely diversion of material based on predefined criteria.
International Society for Pharmaceutical Engineering (ISPE)	681	681	Annex II	Replace “verified using” with “justified for” lest readers infer that they should use the commercial equipment to repeat experiments investigated in development. This may be feasible for DP CM, but it is not feasible for DS CM.	Appropriate controls and monitoring requirements for the continuous crystallisation were extensively investigated during development in similar, but smaller scale equipment and ~~verified~~ **justified** for commercial equipment.
International Society for Pharmaceutical Engineering (ISPE)	690	690	Annex II	add a statement as warning for scale differences and the need to carefully evaluate quality at both development and manufacturing scales	As development was done at a different scale and as product quality may be affected by scale factors, a better risk-based and science-based justification (e.g., through DOE’s) should be used to support validity of development (small scale) results onto commercial scale.
International Society for Pharmaceutical Engineering (ISPE)	692	693	Annex II	Surge point 1 is after only a single reaction with quench and layer separation, and the flow is truly continuous coming out of liquid-liquid extraction at this point, therefore it should be able to flow directly into the second PFR. We typically would only put a first surge point after an intermittent flow unit operation or after a significant number of unit operations, to provide a decoupling breakpoint. In contrast, in the annex 1 example, there is no obvious reason to justify the first surge point as shown in Figure 1 and described in the text. Surge point 3 is after filtration, which we suggest does not make sense. We suggest changing the part of the process Figure 1 after the continuous crystallizers. Dual filtration, followed by surge point 3, followed by batch filter drying does not make sense. If the first batch operation is filter drying, then slurry flowing from the continuous crystallizers would more likely either (1) flow directly onto one of two parallel filter dryers that switch back-and-forth, or (2) accumulate in a large surge vessel before any filtration, then transfer onto a large single filter dryer, or (3) accumulate in a large surge vessel before any filtration, then transfer to a centrifugal filter and dryer combination. Alternatively, the slurry emerging from the continuous crystallizers could flow into a continuous filter/dryer which continuously discharges dried solids.	We recommend removing surge points 1 and 3 to make the process more realistic. Only surge point 2 makes sense. The corresponding text should be changed. Also, please change dual filters to filter/dryers and discharge dry solids.
International Society for Pharmaceutical Engineering (ISPE)	705	705	Annex II	A backup pump is not going to enable continuous operation without stopping, because it will take a little downtime to switch over to the backup pump.	Use of redundant equipment (e.g., backup pumps) at key locations to ~~enable continuous operation~~ **minimize interruption time.**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	714	718	Annex II		The combination of process controls, online PAT measurements, comprehensive monitoring of process parameters and material attributes, and end-product testing results **in higher levels of quality assurance and a** data-rich environment to this process. Together with system understanding generated during development, process was validated for commercial product launch and then continuous process verification was applied to ensure a state of control through process changes over the product lifecycle.
EFPIA	720	720	Annex I, Section 2.4	This process employs a long run time of several months (line 701). Rationale in column "Proposed changes / reccomendation"	**Description of how batch sizes and durations where primary stability batches were handled would be a useful exmaple to the concepts described in section 4.5.** **For EWG Discussion**
EFPIA	725	725	Annex 1	Current wording stating "similar equipment" could be interpretted to mean similar scale. As noted in line 682 development work can and did occur in smaller scale equipment in this example. Suggest alternate wording in order to eliminate confusion and ensure clarity and consistency in this example and how drug substance CM systems could very likely be developed. Rationale in column "Proposed changes / reccomendation"	**Modify to say "This included work on representative equipment ..."**
International Society for Pharmaceutical Engineering (ISPE)	725	725	Annex II	Add the words "smaller scale" to avoid readers misinterpreting "similar equipment" to mean similar scale. It may be feasible for drug product CM to do development work at similar scale to manufacturing scale, but it is not feasible for drug substance CM.	This included development work on similar **smaller scale** equipment
International Society for Pharmaceutical Engineering (ISPE)	729	730	Annex II	In this drug substance process, shown in Figure 1, the filter-dryer sets to batch size. Extension of run time would most likely increase number of batches per single continuous run, not increase batch size	Subsequently, a continuous process verification approach was adopted after product approval to support increases in **number of batches** with extension of run time
International Society for Pharmaceutical Engineering (ISPE)	731	731	Annex II	It is easier and convincingly stronger to demonstrate and claim that process performance is unaffected by run time differences, if the control strategy remains valid and effectively ensuring consistency of output material quality.	for the longer run time, which concluded that ~~process performance~~ **existing control strategy performance and output** material quality would not
BioPhorum	747	748		This is the language used for other ICH annexes, specifically ICH Q12. Please align.	The discussion points presented here for drug product CM systems are mock examples provided for illustrative purposes.
APIC	747	748	Annex II, 1	This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The discussion points presented here are not exhaustive for solid dose drug product systems. Alternative approaches can be used."	Change please to: "The discussion points presented here for solid dose drug product systems are mock examples provided for illustrative purposes." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)
EFPIA	752	759	Annex II, Section 1.	Provide an update to Figure 2 to represent a regulatory flow diagram to serve as an example for authors. Rationale in column "Proposed changes / reccomendation"	**For EWG Discusson**
BioPhorum	764	765			The CM system and its control strategy were designed to mitigate the impact of disturbances to ensure **process performance and output material quality through the definition of acceptable ranges and target values.**
International Society for Pharmaceutical Engineering (ISPE)	769	769	Annex II	We suggest swiching the order of the words development and design, since design precedes development	During process design and development, a quality-by-design approach was adopted that identified

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	796	796	Annex II, Section 2.	Editorial: "Modelling", uses British spelling, where American spelling has been used throughout the document. Rationale in column "Proposed changes / reccomendation"	**Consider using "Modeling".**
International Society for Pharmaceutical Engineering (ISPE)	796	796	Annex II	Funnel plots alone are not a statistical analysis, but rather a graphical depiction of the outcome of statistical modelling	**Statistical modelling was** used to help determine limits for the magnitude and duration of disturbances in mass flow rates, for which material diversion operator investigation, or process stop are needed. **These limits can be visualized for ease of use (e.g. funnel plots).**
EFPIA	851	853	Annex II, Section 2.4	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. Rationale in column "Proposed changes / reccomendation"	**Please clarify continuous process verification approach. Description of how the run time extensions beyond current experience were validated would provide a great example. For EWG Discussion**
International Society for Pharmaceutical Engineering (ISPE)	859	978	Annex III		Annex III is written as a guideline and not as an example. While Figure 3 shows a flow diagram for an example, it is not discussed in the text. It is recommended to move the essential and non-redundant aspects of Annex III to the core document and delete the Annex or replace it with a true example.
BioPhorum	862	866		This annex augments the main guideline by providing additional considerations specific to CM processes for therapeutic protein drug substances **OR** drug substances used as intermediates for subsequent conjugation. It describes aspects that could be applied in fully or partially integrated CM systems. The discussion points presented below are not exhaustive. Alternative approaches can be used.	Why include PEGylation when not referred to in the Annex. This seems like a specific example, but then the rest of the text is not specific to a perticular process. Can we change the example or add more detail on the process, if PEGylation continuous?
EFPIA	864	864	1	Usage of incorrect terminology "drug substances used as intermediates for subsequent conjugation". These are not technically drug substances. In this case, the conjugated protein would be the drug substance, not the intermediate prior to conjugation.	**Change "drug substances used as intermediates" to "intermediates (e.g., monoclonal antibodies".**
BioPhorum	866	867		This is the language used for other ICH annexes, specifically ICH Q12. Please align	The discussion points presented here are mock examples provided for illustrative purposes.
EFPIA	866	867	Annex III, Section 1	Annex III, Section 1 This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The discussion points presented here are not exhaustive. Alternative approaches can be used."	Change please to: **"The discussion points presented here are examples provided for illustrative purposes." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)**
APIC	866	867	Annex III, 1	This sentence is not clear, especially with the term "exhaustive." This sentence is also not aligned with other ICH annexes, such as ICH Q12 annexes. "The discussion points presented here are not exhaustive. Alternative approaches can be used."	Change please to: "The discussion points presented here are mock examples provided for illustrative purposes." (This is the language used for other ICH annexes, specifically ICH Q12. Please align.)
BioPhorum	870	870		Although not as detailed as may be required in the CTD application, section 3.2.S.2.2 Description of Manufacturing Process and Process Controls for biotech (ICH M4Q), the information is a good high level representation.	Either remove the sentence or replace with: It should be noted that a process flow diagram to document in the CTD, section 3.2.S.2.2, for the biologic drug substance would be more detailed than the one shown below.
EFPIA	870	870	Annex III, Section 1	Please remove the following text: "It is not intended to represent a regulatory flow diagram." Although not as detailed as may be required in the CTD application, section 3.2.S.2.2 Description of Manufacturing Process and Process Controls for biotech (ICH M4Q), the information is a good high level representation. Rationale in column "Proposed changes / reccomendation"	Remove sentence please. If needed, please add in **"It should be noted that a process flow diagram to document in the CTD, section 3.2.S.2.2, for the biologic drug substance would be more detailed than the one shown below."** **FOR EWG DISCUSSION**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	870	870	Annex III, 1	Please remove the following text: "It is not intended to represent a regulatory flow diagram." Although not as detailed as may be required in the CTD application, section 3.2.S.2.2 Description of Manufacturing Process and Process Controls for biotech (ICH M4Q), the information is a good high level representation.	Remove sentence please. If needed, please add in "It should be noted that a process flow diagram to document in the CTD, section 3.2.S.2.2, for the biologic drug substance would be more detailed than the one shown below."
BioPhorum	878	880		It seems like a single thaw = a single batch, while a multiple thaw = multiple batch, even though that is not the case. There is also no specificity regarding cell bank - is it working or master?	In CM processes, a single thaw of one or multiple pooled vials from the same working or master cell bank, may result in either a single harvest or multiple harvests. A science and business risk **assessment, along with the process control strategy, will lead to decisions on determining the number of cell bank vials correlated to the number of harvests and batches.**
APIC	878	880	Annex III, 1	This statement is not clear. It seems like a single thaw = a single batch, whicle a multiple thaw = multiple batch, even though that is not the case. There is also no specificity regarding cell bank - is it working or master? "In CM processes, a single thaw of one or multiple vials from the same cell bank may result in either a single harvest or multiple harvests. This produces a single batch or multiple batches of drug substance."	Rewrite please as:"In CM processes, a science and business risk assessment, along with process control strategy, will lead to decisions on determining the number of working cell bank vials correlated to batch size"
EFPIA	882	884	1	Figure 3 only shows one PAT/diversion point, beween chromatography #1 and surge tank and it is also not described in the text. Rationale in column "Proposed changes / reccomendation"	**Add existence of potential PAT / diversion points (e.g., after cont. capture) in text**
APIC	882	883	Annex III, 1	Regarding Figure 3, there is legend: T1: PAT and D1: Diversion point, but T1 and D1 are not reported in the figure.	Please include also T1 and D1 in figure 3.
International Society for Pharmaceutical Engineering (ISPE)	886	889	Annex III	This also apply to 972-978 This section includes guidance and should be in the core document.	Recommend to move to a new section in 3.1 Control strategy. Note that some of this advice is equally applicable to sterile small molecule manufacturing.
EFPIA	889	970	General	Frequent use of the word "should" in Annex III could be taken to imply a requirement, very different language from that used in the examples in Annexes I and II, where the language used is "was done', "was described", etc., consistent with the idea of illustrative examples, not binding requirements in the Annex examples. Rationale in Column "Proposed changes / reccomendation"	It's okay to use "should" where there is a firm requirement arising from other ICH guidelines, but the language in Annex III should be changed otherwise to avoid the reader seeing the details of the Annex II example as binding requirements for CM of biopharmaceuticals.
BioPhorum	896	897		The original statement is not in alignment with QbD principles, as highlighted in ICH Q8. Please update to remove "measures" and "testing" or clarify with the design control principles, rather than testing.	**During early development, evaluation by risk assessment, process understanding and testing are encouraged to demonstrate the acceptability of all cell culture material used to generate a given drug substance batch. New technologies for real-time decision-making, such as rapid testing for adventitious agents are encouraged when the design control strategy is not in place to mitigate the impact of contamination events during continuous operation.**
EFPIA	896	899	Annex III, Section 2	This statement is not in alignment with QbD principles, as highlighted in ICH Q8. Please update to remove "measures" and "testing" or clarify with the design control principles, rather than testing. Statement of concern: "This means that measures should be in place to demonstrate the acceptability of all cell culture material used to generate a given drug substance batch. Rapid testing for adventitious agents, when possible, may enable real-time decision-making to mitigate the impact of contamination events during continuous operation." Rationale in column "Proposed changes / reccomendation"	Recommend changing sentence to**: "During early development, evaluation by risk assessment, process understanding and testing are recommended to demonstrate the acceptability of all cell culture material used to generate a given drug substance batch. New technologies for real-time decision making, such as rapid testing for adventitious agents, are recommended to mitigate the impact of contamination events during continuous operation."**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	896	899	Annex III, 2	This statement is not in alignment with QbD principles, as highlighted in ICH Q8. Please update to remove "measures" and "testing" or clarify with the design control principles, rather than testing. Statement of concern: "This means that measures should be in place to demonstrate the acceptability of all cell culture material used to generate a given drug substance batch. Rapid testing for adventitious agents, when possible, may enable real-time decision-making to mitigate the impact of contamination events during continuous operation."	Change please to: "During early development, evaluation by risk assessment, process understanding and testing are encouraged to demonstrate the acceptability of all cell culture material used to generate a given drug substance batch. New technologies for real-time decision-making, such as rapid testing for adventitious agents are encouraged when the design control strategy is not in place to mitigate the impact of contamination events during continuous operation."
International Society for Pharmaceutical Engineering (ISPE)	900	924	Annex III	This section includes guidance and should be in the core document	Recommend to include in Section 3.1.4 Equipment Design and System Integration
BioPhorum	901	903		The original statement implies that a large burden of work must be down to "ensure" the integrity of single-use equipment prior to use. Please update based on risk assessment approach, with factors including application, risk of contamination and other factors.	The use of closed processing equipment has been shown to decrease the risk of contamination from adventitious agents. Whether single-use or stainless steel equipment is used, its integrity during use should be ensured to prevent contamination. Appropriate testing (location and detection assay) should be in place, reflecting the risk of contamination.
APIC	901	903	Annex III, 2.2	This statement implies that a large burden of work must be down to "ensure" the integrity of single-use equipment prior to use. Please update based on risk assessment approach, with factors including application, risk of contamination and other factors. "While the use of closed processing equipment may decrease the risk of contamination from adventitious agents, the integrity of single-use equipment during use should be ensured to prevent contamination."	Please update text as follows: "The use of closed processing equipment has been shown to decrease the risk of contamination from adventitious agents. Single-use equipment is encouraged. Testing should be correlated with the risk of contamination."
BioPhorum	903	904		Too specifc to single use technology and needs to refer back to the risk assessment.	The potential weak points (e.g., welds, connectors) and typical locations where systems require changing out over a potentially extended time frame or at a higher frequency for a CM process should be evaluated by risk assessment for potential contamination risks and mitigation measures should be identified.
EFPIA	914	914	Annex III, Section 2.2	Editorial - The wording, "inadvertant contamination" is superfluous. Rationale in column "Proposed changes / reccomendation"	**Consider removing "inadvertant".**
EFPIA	918	919	Annex III, Section 2.2	Editorial - The phrase, "between steps such as virus inactivation" is an incomplete example. Rationale in column "Proposed changes / reccomendation"	**Consider replacing with "between unit operations"**
International Society for Pharmaceutical Engineering (ISPE)	925	937	Annex III	This section includes guidance but is redundant with core document	Recommend to delete as it does not contain any new information
BioPhorum	939	940		Call out validation on the linkages between unit ops as well as the unit ops themselves	Process validation approaches used for processes run in batch mode are also applicable to CM processes and may be agumented with validation of the process orchestration, fatigue and movement of material.
International Society for Pharmaceutical Engineering (ISPE)	939	958	Annex III	This section provides guidance and should be in the core document	Recommend to move paragraph 944-951 to core document, section 4.7 and to delete the rest (939-946, 951-958)
EFPIA	949	949	3.1	Vague terminology "process qualification" What is meant by "process qualification"? Is it simply "process validation? If so, we need to update the language.	**Change "process qualification" to "process validation" unless that is not what is meant.**

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	957	957	3.1	"sufficiently alike" is an unusual word choice. We aren't looking for molecules that are alike, we are looking for those which are similar.	**Change "sufficiently alike" to "sufficiently similar".**
International Society for Pharmaceutical Engineering (ISPE)	959	971	Annex III	This section includes guidance and should be in the core document	Recommend to incorporate into Section 3.2
International Society for Pharmaceutical Engineering (ISPE)	979	1144	Annex IV		Annex IV contains guidance like material related to integrated small molecule/drug product processes which is outside the scope of an example. Sections should be rewritten to be consistent with a case-specific example.
EFPIA	1012	1013	2.2	Figure 4: Blender before the tablet press is not adding value to the process and hence should be removed to avoid confusion. Blender prior the tablet press would only be required if an additional excipient is added here as outer phase.	**FLOW CHART MODIFICATION** Remove blender. The example does not include an outer phase, therefore the blender is not required before the tablet press. No addtional exciepients are added in the final blend **(Add to Text, Not currently stated)**
EFPIA	1012	1013	2.2	Figure 4: Replace "Comill" with "Mill" to avoid confusion "Comill" is widely known as Mill Manufacturer using conical milling principle mainly. In this example a oscillating mill is used. Anyway, the type of mill is not important for the figure, hence only "mill" or "sieve mill" should be stated here.	**FLOW CHART MODIFICATION**
EFPIA	1024	1024	2.2	The desciption of process design only focusses on the DS manufacturing part - does not describe any details on DP manufacturing part From consistency view, it would be good to add a sentence here as well for the DP process design	**API slurry after filtration is combined with excipient stream in the wet granulation step using twin screw extruder. Resulting granules are dried, milled and compressed to tablets followed by subsequent coating. PAT ports (T2/T3/T4/T5) allow monitoring of critical quality attributes, e.g. API concentration, blend- and content uniformity , residual moisture or particle size. Diversion ports D2/D3/4 may be used to divert non-conforming material accordingly.**
EFPIA	1042	1051	2.4	Compared to example in Annex II - the level of detail in Annex IV is low. Complete section 2.4 and 2,4 is written very high-level and without any clear description of the implemented approach for start-up/shut sown or RTD evaluation From consistency view, it would be good to add more information into section 2.4 and 2.5 about the implemented approach for start-up / shut down or RTD evaluation. Especially when compared with Annex II, level of information in Annex IV is very general.	**Describe more details on how start-up / shut down procedure was / is implemented and how RTD is evaluated in DS and DP process. Refer to other Annex (e.g Annex II) in case same approach is used**
International Society for Pharmaceutical Engineering (ISPE)	1066	1096	Annex IV	In certain places, the language is guidance-like and not appropriate for an example. Recommend some simple changes (mostly verbs) to make this a specific example rather than general guidance expectations. Alternatively, if the intent is to keep this guidance-like language, the sections should be moved into the main text and not under the guise of an example.	A few examples 1068 change “should be” to “was” 1079 change “should” to “would” 1082 change “can” to “would” 1119 change “can be” to “is” 1126 change “could be” to was” 1133 change “may be appropriate” to “was additionally used”
International Society for Pharmaceutical Engineering (ISPE)	1084	1084	Annex IV	Expanding slightly to provide a more clear sentence.	conditions, or other factors **identified using** risk-based considerations.
Gilead Sciences	1087	1090	Annex IV, 3.1	Is the testing of the drug substance at location T1 considered as a real-time release testing (RTRT)? If not, please clarify whether a product release is required for drug substance in an integrated CM process.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	1092	1092	Annex IV	We recommend being explicit about what is meant by 'discussion'.	Although the drug substance is not isolated, a ~~discussion~~ **justification science- and risk-based** of the origin and fate of potential
International Society for Pharmaceutical Engineering (ISPE)	1098	1104	Annex IV	We recommend rewording to be supportive of an example rather than guidance	"In **this** integrated processes, attributes typically associated with the drug substance quality ~~are generally~~ **were** included in the drug product specification ~~unless justified~~ ~~per~~ **consistent with** ICH Q6A. Therefore, the drug product specification **for the** ~~in an~~ integrated process is more extensive than that of a batch process and ~~may~~ includes drug substance related substances, residual solvents (used in drug substance synthesis), elemental, impurities, etc., ~~when appropriate~~. The specified impurities in the drug product specification may differ from the specified impurities in the drug substance specification (e.g., mutagenic impurity)
International Society for Pharmaceutical Engineering (ISPE)	1131	1132	Annex IV	Absence of hold data does not automatically require disposal of the material. Rather, an investigation should be launched which may involve collection of data.	~~In the absence of data to support a hold time, drug substance formed during a process interruption should be discarded~~
International Society for Pharmaceutical Engineering (ISPE)	1137	1144	Annex IV	This section has important guidance content that Is independent of the example; it should be moved to the core document	Recommend to move to section 4.1 in core document
International Society for Pharmaceutical Engineering (ISPE)	1145	1277	Annex V		The last annex (V) on managing disturbances is not very informative (basic and not developed in detail), recommend adding more details.
International Society for Pharmaceutical Engineering (ISPE)	1169	1169	Annex V	The proposed change would make it clear that the direction doesn't matter, just the magnitude deviation from 100%. Even though this is an example, it could lead readers to implement better, more useful graphics if the example is a better one.	Color scheme gradient that varies from 100% to <90% and uses the SAME color gradient from 100% to >110%
EFPIA	1191	1191	Annex V	Disturbance acceptance criteria should be "80 seconds" instead of "80 minutes".	**Change to seconds**
EuropaBio	1191	1191		Could be a typo in the specific criteria for disturbances	The amplitude value (+/- 20%) seems correct, but the time (80 minutes) seems way too long, relative to the funnel plot example (could it be seconds rather than minutes?)
EuropaBio	1204	1204		If the funnel plot indicates the material is well within range, is the additional quality check necessary? If yes, then what is the purpose of the funnel plot to begin with?	Suggest updating to indicate that a quality check or additional controls could be considered (e.g. NIR, process model, or even the diversion strategy being set to limits well inside of the 90-110 limit). There should be a point when the funnel plot has value - for e.g. when manufacturers are well within limits. In this case, additional checks should not be required.
International Society for Pharmaceutical Engineering (ISPE)	1235	1236	Annex V	The example and is described as an "infrequent transient flow" (line 1220). If such a disturbance was expected and described in operational procedures, no investigation would be needed	**In most cases,** a concurrent investigation ~~should~~ **would** be initiated to determine the root **cause of the disturbance**.