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<Date of submission>

Submission of comments on ICH guideline Q13 on continuous manufacturing of drug substances and drug products Step 2b EMA/CHMP/ICH/427817/2021

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
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All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
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Name of organisation or individual*	Line from* (line Nr or 0 for general comment	Line to* (line Nr or 0 for general comment	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
International Society for Pharmaceutical Engineering (ISPE)	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			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.
International Society for Pharmaceutical Engineering (ISPE)	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.
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
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 .
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.
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.**
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 ...
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.

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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….
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):
International Society for Pharmaceutical Engineering (ISPE)	286	286	3.3	To improve the statement accuracy and readability.	parameters relevant to process dynamics and **output** material quality
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"~~
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.
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)
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)"~~
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
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.**
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
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.

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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.**
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.
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).
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"**
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…"
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.**
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,
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~~.
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
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

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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.
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."
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**
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
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.
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.
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.**
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

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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.**
International Society for Pharmaceutical Engineering (ISPE)	645	645	Annex I		with minimal impurity formation is ensured through control of the reaction temperature **and time**
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.
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.
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.

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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.**
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.
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
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
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).**
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.
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
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
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

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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)
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.
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.
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)					
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%
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**.