September 21, 2017

US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852
via electronic submission

Subject: **Docket No. FDA-2017-N-2697** for "Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing"

Dear Sir or Madam:

ISPE (the International Society for Pharmaceutical Engineering) would like to submit comments for the FDA docket "Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing." ISPE applauds the agency's reception of general input in addition to specific comments on the two documents mentioned within the docket.

The structure of the comments is to provide ISPE's view of the desired content of a future FDA or international guidance on continuous manufacturing for solid oral dosage forms. Where appropriate, references are made to the documents referenced in the docket. The comments were prepared by a group of industry leaders in the field with a broad input across the global ISPE membership.

ISPE is a not-for-profit organization of more than 18,000 individual members reflective of technical, engineering, quality and operational activities throughout the product lifecycle. The Society has been facilitating dialogue on continuous manufacturing between industry and regulators at more than a dozen ISPE conferences from 2011 through September of this year. In April 2016, ISPE produced a dedicated continuous manufacturing conference which was co-chaired by FDA and attended by industry professionals from 13 countries. ISPE remains committed to lending its expertise on this topic and will continue to support industry and regulators through its education programs towards implementation.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Sincerely,

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ISPE CEO and President

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ISPE Comments on Docket No. FDA-2017-N-2697: "Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing"

General Definitions & Principles	Document Reference	Suggested Considerations for Guidance	Background/Justification/Concerns
Definition of continuous	CSOPS Section 2.1, paragraph 1 - Disagree	A guidance on continuous manufacturing (CM) should specify its scope, e.g. "at least 2 integrated unit operations where process dynamics considerations impact the monitoring, sampling and/or release of product." Such a definition should be applicable for SODs or other applications, like API and biotech products.	The CSOP definition of continuous manufacturing as, "multiple, highly integrated unit operations operating synchronically at the same rate" is too specific. It does not account for situations such as partial accumulation of material between steps (e.g., a segmented drier) or for a process that has some continuous and some batch steps (e.g., batch preblending or a batch coater). The CSOPs document in Section 2.1 also mentions that in CM the operation is not interrupted; however, process pauses are possible with CM. We recommend including in the scope of a CM guidance only processes where process dynamics are important; regulatory considerations for other processes remain the same as for traditional batch (e.g., multiple API synthesis steps followed by batch crystallization).
Definition of "batch"	CSOPs Section 2.2.2, paragraph 3 – Agree, with additional comments	The bullets describing the options for defining a batch are suitable with the caveat that "irrespective of the time taken" in the second bullet is only appropriate with suitable process controls and process validation.	Flexibility in defining "batch" is important for encouragement of this new technology.

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State of control vs. steady state	CSOPS Section 2.1, paragraph 5 –Disagree MIT Section 2.1.2.1 – Agree, with additional comments	Obtaining a "state of control", as defined in ICH Q10, is sufficient to achieve product quality for continuous manufacturing. Steady state will frequently be observed but is not required to ensure product quality.	Steady state is a theoretical concept in engineering to understand and model processes and is not utilized in process control. Good quality product can be achieved with reproducible transient operation for processes that are well understood, such as during a controlled start up or shut down. Steady state alone does not assure manufacture of good product. Defining steady state for continuous manufacturing could take much effort and resources without benefit to product quality.
Requirement for PAT and RTRT in continuous manufacturing	Not specifically discussed	The guideline should acknowledge that based upon product and process risks, PAT for inline monitoring may not be needed. The need for redundancy of PAT tools should be addressed based upon risk assessment of product & process as related to the patient. Additionally, although CM can lead to more RTRT, it should be clarified that RTRT is not a requirement for a CM process.	Requiring PAT for inline monitoring and/or RTRT for all continuous manufacturing operations could discourage or slow adoption of this technology. Voluntary use of PAT tools and RTRT is consistent with FDA's PAT Guidance.

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Fundamental Engineering Concepts and Definitions	CSOPs, Section 2.1	A guidance document should include how the aspects related to fundamental engineering concepts can be implemented and expressed for pharmaceutical manufacture. Process knowledge, including the functional relationships between process terms and the quality attributes that they impact should be identified and discussed (including their control) to ensure product quality is maintained. The control of CPPs and CQAs should be included in the Control Strategy. Terms defined in this section should be included in a glossary.	Although this section in the CSOPs document is good a summary of engineering concepts and background/ introduction information associated with continuous manufacturing, it is too academically and technically oriented to be a useful guidance document.
Established Conditions	Not discussed	Without being too prescriptive, a guidance document should identify what process parameters and quality attributes should be established conditions and included in P.3.3. It should also state what information should remain in P.2 as justification of process parameters ranges, IPC's and release testing.	With the advent of ICH Q12, future guidance should discuss established conditions as related to continuous manufacturing and to clarify what established conditions mean to ensure alignment.
Control Strategy Definition & Design	**Document Reference**	**Suggested Considerations for Guidance**	**Background/Justification/Concerns**
Potential for both batch and continuous manufacturing in the same application	Not discussed	The guidance should explicitly address that both continuous and batch manufacturing can be in the same application. Considerations from a patient perspective are that both the batch and continuous drug products should be indistinguishable from the	Both continuous and batch manufacturing processes be allowed in the same dossier is supported by ICH Q8/9/10 Points to Consider, Section 3.1, "Different Control Strategies for the Same Product". ICH Q8(R2) does not explicitly include the concept of a "formulation design

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		patient based on appearance, product performance, and labeling (e.g., inactive ingredients). In general, the quality standards for products made from the two processes remain the same, but that the specific tests and related acceptance criteria may vary. Flexible formulation should be possible with different compositions for batch and continuous manufacturing for the same drug product, to enhance process consistency and robustness.	space" but such an approach can be supported scientifically. Forcing both continuous and batch manufacturing to have the same formulation could lead to higher product variability and lower process robustness. As the science and technology progresses, fully adjustable formulation design spaces could support adjustable formulations to provide the most consistent product performance, using a feedforward approach.
Process Development: Determining Process Dynamics/ RTDs	CSOPS Section 2.1, paragraph 10 - Agree	The document appropriately describes the topic.	Knowing the characteristic time for individual unit operations, groups of unit operations as well as the entire system can be useful for process understanding and potential future updates or transfers.
Process Development: Assessing Impact of Material Variability	MIT Section 2.1.2.1 - Agree	The document appropriately describes the topic.	A USP Chapter for standards for CM is in development and could serve as a reference for future FDA guidance.
Risk assessment & failure mode analysis	MIT Section 2.1.2.1, Paragraph 8 – Agree, with additional comments	CM control strategy development should follow ICH framework for risk assessment, such as FMEA, but would typically rely more on modeling/simulation. In addition to assessing the risk of process parameter variability on finished product quality attributes, consideration should be given to risk associated with implementation of the control strategy, such as risks associated with setting up PAT methods and equipment design.	Consideration should be given to other types of failure modes when implementing the control strategy.

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Raw material specifications	CSOPs Section 5.2.1 – Paragraph 3&10 – Agree, with additional comments	While specification setting for drug substances and excipients will based primarily upon prior experience, it should be permissible to have wider specification ranges, especially when supported by risk assessments and/or a material monitoring program within the quality system that evaluates the impact of material outside of the previous experience range.	Setting specifications too tightly because of limited experience could lead to unnecessary restrictions or excessive future supplements. Evaluation of future material variability can generally be handled within the quality system.
Sampling for assay and content uniformity	CSOPs Section 3.2.1 – Agree, with additional comments	The guidance document should clarify that the applicant should define sampling location, size, and frequency based upon ability to identify and divert potentially non-conforming material as determined through failure mode analysis and risk assessments. Sampling frequency should be linked to the process dynamics and controls in combination with the proper statistical methods, not the total run time. Addressing large sample sizes and related acceptance criteria is an important part the guidance, including if the FDA will accept the Large N chapters from the European and/or Japan Pharmacopeias.	Clear definition of acceptance criteria for large sample size and varied batch size is needed. Forcing continuous manufacturing sampling to have the same acceptance criteria as batch manufacturing and/or a zero failure criteria could deter adoption of CM and does not match with reality of CM.
Sampling for dissolution	Not discussed	Sampling for dissolution, including location, size, frequency and the need for stratified sampling should be based on risk assessments. It would be expected that only high risk situations would require routine stratified sampling to meet the dissolution specification.	

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Models and simulations	Not clearly discussed	A future guidance should clearly delineate that models (soft sensor, PAT, MVA etc.) for CM can play different roles and may be used in development, tech transfer, troubleshooting, monitoring, control and optimization in commercial manufacturing. The model verification and dossier details should vary according to the use of the model, consistent with the ICH Q8/9/10 Points to Consider document.	Examples of process development models include: off line models for process understanding, equipment characterization, unit ops and flow sheet simulations, in-silico models. Examples of multivariate/chemometric models for PAT include NIR, Raman. Examples of models for monitoring and control include: SPC/MSPC, soft sensors, latent variable modeling, RLS, etc. Soft sensors (mathematical models based on process parameters /quality attributes)) can be a much cheaper, easy-to-maintain, and maybe more robust in practice than a PAT method that directly measures the attribute.
Advanced Process Control	Refer to an article on GMP implementation of APC system in tablet manufacturing, APR, Huang et.al, March 2017, Vol20, Issue 2	To make a future guidance forward looking, it should include discussion of Advanced Process Control (APC). Although the industry is not there yet, CM also brings opportunities for level 3 control strategy (e.g., model based control) using APC. Consider referencing ISA-95 standards for control system architecture.	Advanced Process Control sits at the supervisory control layer (on top of regulatory control layer), orchestrates local PID controllers, controls and optimizes processes in a closed-loop. Key APC components could include PAT, soft sensors, control models and real-time optimizers. CM benefits from APC for improving quality, throughput and yield. APC has been already successfully implemented at some companies for commercial batch manufacturing.

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Material Diversion – Model impact	Not discussed	Material diversion is a holistic control supported by models/ automation/ equipment design to support the diversion strategy. Not all models for diversion are necessarily high impact, as with the presence of redundant measurements. For example, an NIR model for blend uniformity that triggers diversion is redundant with a high frequency content uniformity measurement at the tablet feed frame. Typically, the latter measurement would be used for release decisions and deemed to be a high impact model.	FDA has suggested that any models used for quality decision, including diversion to waste would be considered high Impact. However, if the model is redundant with other controls and tests (including diversion models), it should be considered moderate impact, as based on the Q8/9/10 Points to Consider document.
Off line and alternate testing /contingency plans when PAT is not available	MIT Section 3.8.4 – Agree, with additional comments	Traditional testing should be allowable as an alternate control strategy, if justified and validated. Typically, a decision tree would be available as part of implementation of the control strategy to support decision making.	Alternative release testing approaches should be allowed for scenarios where PAT is not available.
Data storage & handling	CSOPs Section 2.2.4, with additional comments	A CM guideline could simply reference current guidelines on data handling and storage system requirements. Additionally, if material characterization is required as part of RTRT, new methods of integrating data from multiple data sources may be required.	Although the handling and storage of data should follow current guidelines, the nature of CM will generate much larger amounts of data and require more complex automation systems to handle PAT, soft sensors and APC. Clarification is needed from the Draft Data Integrity Guideline if non-reduced data from PAT systems needs to be retained. Such a requirement could be problematic from a data storage perspective.

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Clinical Supplies/ IND Phase	Document Reference	Suggested Considerations for Guidance	Background/Justification/Concerns
Information in IND process description	CSOPs Section 5.1, Agree	The document appropriately describes the topic.	
Specifications & tests during IND phase	CSOPs Section 5.1, Agree, with additional comments	In addition to stating that PAT methods will evolve during development, it would be useful to mention that some PAT could be used for development activities but may not be included in the control strategy.	Sampling frequency should be flexible and fit for purpose; at minimum it should ensure patient safety for clinical trials
Bridging expectations	CSOPs, Section 6.2.3; MIT, Section 4 - Agree with additional comments	Clarity is needed related to when a change of scale or equipment requires bioequivalence and/or stability studies (e.g., change of scale, site change, switch from batch to continuous blender).	For situations when process development coincides with clinical supply manufacture, flexibility in the IND manufacturing process is necessary in order not to impede further process development.
Hybrid continuous/batch processing and traditional testing in early development	Not discussed	The guidance document should explicitly discuss allowances for hybrid approaches and traditional testing in early development. For example, a process with collection of all material from a continuous blender prior to the next operation and using off-line HPLC could provide early clinical material and the data could be leveraged for later stage activities.	Industry is concerned that the Agency will expect continuous manufacturing and PAT throughout development. Currently, very small scale CM equipment is not available and/or correlated with larger scale equipment.

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Commercial implementation, validation and verification	Document Reference	Suggested Considerations for Guidance	Background/Justification/Concerns
Batch traceability for batch release and deviation management	MIT Section 2.1.2.1, 3.2, 3.6 - Agree	The document appropriately describes the topic. The guidance could also reference ASTM E2968 related to this topic.	
Collection of material during Start up and shut down & pauses	CSOPs Section 3.2, paragraph 4 – Agree with additional comments	The guidance should discuss how the quality system should define when it is acceptable to collect product during start up. Pauses in the system should be validated to determine how much, if any, product needs to be diverted upon restarting. In some cases, it may be appropriate to collect product during a portion of a controlled shut down (when part of the system has emptied) if acceptable product is being manufactured.	
Potential acceptance of diverted material	MIT Section 3.2, paragraph 2 -Agree with additional comments	The language could be clearer related to potential acceptability of diverted material. Considerations should include whether the material is appropriately segregated and if the definitive root cause of the diversion is determined from the investigation.	
Handling Deviations	MIT Section 3.8 – Agree, with additional comments	The guidance should clearly state that not all diversions will constitute a deviation. For example, diversions during normal start up and shut down are not deviations. Additionally, any deviation should be resolved prior to release of batch. The guidance could also reference ASTM E2968 related to this topic.	The MIT paper nicely states, “The process control/monitoring system shall be adequately developed to recognize a normal process, and be able to identify when the data are divergent enough to represent a departure that could have direct impact on quality.” It is important to differentiate diversions under normal operation vs. atypical operation.

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Considerations for number of PPQ start-ups, shut downs and batches	MIT, Section 3.5 – Agree with additional comments	The guidance should provide considerations on how to determine how much PPQ data is needed, especially when using a continuous verification approach. Additionally, the guidance should clarify how the Agency considers **continuous** process verification approach to correlate or interrelate to Stage 3 **continued** process verification. The Agency should consider adopting the European term of "ongoing process verification" instead of "continued process verification" to minimize confusion between "continued" and "continuous" process verification.	For new products, it is likely that extensive commercial experience will be gained through manufacture of clinical batches which can be leveraged for PPQ. This scenario lends itself to the concept of a single batch or single run PPQ, given sufficient knowledge and understanding of the process, especially when using a continuous process verification approach. Additionally, much confusion currently exists between the ICH concept of "continuous process verification" and FDA's term of "continued process verification".
Equipment and automation IQ/OQ/PQ	Not discussed	Same considerations as traditional batch manufacturing	
Cleaning validation and dedicated/non-dedicated equipment	MIT, Section 3.9 - Agree	The document appropriately describes the topic.	
PAT models and analytical methods verification Soft sensor model and APC validation CMO oversight	Not clearly discussed Not discussed	The guidance should refer to or reiterate the concepts of model development as presented in the Draft NIR guideline. Typically, a decision tree is available in manufacturing for dealing with operational and PAT failure modes. Same considerations as traditional batch manufacturing	Soft sensor method validation follows a similar approach to PAT method validation

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Lifecycle Maintenance & Change Management	Document Reference	Suggested Considerations for Guidance	Background/Justification/Concerns
PAT Model updates		Clarify expectations for reporting of routine model maintenance and updates, either through the NIR Guideline or a CM Guideline. Reporting of routine model maintenance, such as addition of calibration samples, is non value added to industry and the Agency. As ICH Q12 moves forward, please consider use of the PLCM Post-approval CMC commitments section or alternatively use of Performance Based approaches to allow maintenance of models within the quality system with no reporting.	Multiple model updates by regulatory filings are burdensome for industry and of limited value for the Agency. The current NIR draft guidance document is not clear on what level of model maintenance can be managed without reporting in a supplement or within the Annual Report.
Reverification or Revalidation of Models Monitoring & Trending (w/in or between batches)	Not discussed CSOPs, Section 2.2.1 – Agree with Additional comments	The need to reverify or revalidate RTD and/or PAT models over time should be based upon a risk assessment, including when changes are introduced (e.g., compositional changes, flow rate changes, new equipment.) Process monitoring (within a batch or between batches), can be beneficial to determine potential drift or excursion of the individual CPP or multivariate trends,. This monitoring is done within the quality system and not a component of the dossier.	

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Raw materials monitoring / supplier management	Not specifically discussed	Variability of raw material over time can impact the CM process and/or analytical method performance. A monitoring system within the PQS can be used to help identify changes of higher risk raw material and proactively identify their impact. Such an approach could allow for continued product quality while avoiding unnecessarily tight specifications on the raw materials.	
Changes in process design space or NORs/PARs	Not discussed	It may be necessary to reevaluate the RTD, PAT resolution, sampling rate, and system operability (e.g., raw material flowability) when changes occur beyond ranges previously examined, such as for changes in flowrates/throughputs.	
Changes to equipment or site – stability and bioequivalence expectations	CSOPs Section 2.2.2, page 6 - Agree with additions	The CSOPs rationale around the 10x rule not being applicable to CM (in Section 2.2.2, page 6) is true for both bioequivalence and stability considerations. A risk assessment approach should be used to determine sampling for both bioequivalence and stability. Only in rare, high risk situations would necessitate stability samples collected from the largest CM batch size or obtained from stratified sampling.	It is unclear how SUPAC paradigm fits in with continuous manufacturing.
Increase in production amount (e.g., scale up)	CSOPS 2.2.2 – paragraph 7-10 – Agree, with additions MIT 2.1.2.1 – Agree, with	The guidance should acknowledge that different production amounts can be achieved by scale up (larger equipment), scale out (number up), higher throughput/flow rate, or extended run time. The guidance should discuss under what circumstances different aspects of the manufacturing process	Regulatory expectations for changes in production amounts are currently unclear.

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	additional comments	should be reassessed, such as process dynamics, RTDs, or verification of design spaces as a result of the change in the production amount.	

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