22 February 2019

Health Product Inspection and Licensing Division
Health Product Compliance Directorate
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via email

Dear Sir or Madam

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on the draft Guide to Validating Drug Dosage Forms GUI-0029.

ISPE is an individual membership Society of more than 18,500 professionals in 90-plus countries involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership. These comments were developed by a global ISPE team of subject matter experts.

We appreciate the opportunity to submit these comments for your consideration.

Sincerely,

John E. Bournas
CEO & President, ISPE

Health Canada Santé Canada

Comment Form

Optional Contact Information:

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Step 1 Enter the title and number of the guidance document for which you are providing comments.

Guide to validating drug dosage forms GUI-0029

Step 2: Complete Table 1 which can be found on the next page by indicating the line number, page number, current text, proposed revision or comments, and a rationale. You may add additional lines as required.

Health Canada Santé Canada

Table 1: Comments Guide to validating drug dosage forms GUI-0029

Line Number	Page Number	Current Text	Proposed Revision or Comments	Rationale
Table of Contents	3	#6, Format suggestion.	Suggest moving the word “other” to the next line.	Formatting
About this Document: Purpose	5	Purpose: “This document is for anyone involved in manufacturing drug products in Canada.”	If this document applies only to those drug products made in Canada - not sold or distributed in Canada – then this is not aligned with the “Scope: section (see Rationale column to the right.)	The “scope” section has a highlighted paragraph which states that “Importers and distributors of drug products must have documented evidence that their vendors meet validation requirements.” Whose validation requirement? Country of origin or Canada? The Purpose and Scope statements are not aligned/clear.
About this Document: Scope	5	None – missing content	Combination products must fulfill the requirements of both this guidance and of applicable medical device guidance.	While a great number of combination products fall under the Aseptic Guidelines (e.g., prefilled syringes) there are many that would not (e.g., powdered inhalers, inhalative capsules, nasal swabs, etc.). It might be appropriate to have an Appendix to address the combined requirements.
Section 3	7	Validation is not a single study - it represents the cumulative knowledge gained during product development and manufacture. Process validation should incorporate a lifecycle approach, linking:	Suggest changing “linking” to “including”	To add clarity, “linking” only applies to the first bullet
Section 5	9	Lifecycle approach Document lacks mention of Continued Process Validation. Refers to Phase 3 as Validation Maintenance.	Add to 5.3.1 Title “Phase 3:…”	There is currently no Phase 3 section in guide

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Table 1, 2nd row, 2nd column	10	(Excessive hold times may be hard to justify or support ~~or support~~ as it might not represent stability data presented to support the proposed shelf life.)	Does this statement imply that a stability batch with the longest allowable hold time is required? If so, why not state it explicitly?	Needs clarification
Section 5.1.4	11	"Knowledge transfer is a key component…"	Change "transfer" to "management".	The use of "transfer" implies that the data is moving from one location to another location. If all data is being generated at one site, there may not be a "transfer". But the data must still be managed as it is communicated from labs generating the data to the departments using the data (e.g. engineering for equipment suitability and manufacturing to actually make it.
Section 5.1.5	11	Development studies are often conducted on laboratory or pilot-scale batches. It is important to ensure that appropriate scale-up studies are conducted. Identifying parameters potentially impacted by scale is an important consideration in the development phase.	Ratio of Scale Up batch to commercial batch should be defined. The scale up batch is generally 10% of the commercial batch size of 100,000 units, whichever is larger. Do you intend scale-up to mean full scale? Or scale appropriate to verify performance of factors impacted by scale, prior to PV?	A standard should be set for the size of the scale up batch so that it is a close approximation of the commercial batch size.
Section 5.2	11	Consistently produces product meeting its critical quality attributes	Consistently produces product meeting its critical quality attributes and process parameters performing as expected	It is important to meet the critical quality attributes for commercial manufacturing and also the ranges set for set for all process parameters such as CPP, KPP, and NKPP is also important.
Section 5.2.1	12	A summary of the site's readiness for the qualification study including the validation status of all analytical methods and the qualification/calibration status of equipment and facilities	The validation status of the analytical methods does not indicate the completion of validation activity of all analytical methods. Do you mean analytical methods fully validated? Can there be exceptions for validation	The validation status of the analytical methods does not indicate the completion of validation activity of all analytical methods. The validation of analytical methods such as bioburden and

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			of analytical methods such as bioburden and endotoxin to occur concurrently with PPQ?	endotoxin may occur during PPQ execution of fill/finish process for some firms.
Section 5.2.2	12	Current text says to "enroll qualification batches into an ongoing stability program"	Suggest modifying that all PPQ batches go on stability with no distinction between new products and processes undergoing change. "At least 3 PPQ batches should be placed on stability for new products and site to site transfers. A risk based approach should be applied to determine the number of batches placed on stability as the result of a process change."	It would seem there could be some flexibility not to place all PV batches on stability, when the PV is the result of a low risk process change. Also, the number of batches on stability from the same process (pre-PV) could be considered.
Section 5.2.1	12	Protocol, Summaries of CQAs to be investigated and CPPs with associated limits and other non-critical attributes and parameters which will be monitored	Suggest removing "non-critical attributes and parameters"	PV requirement should be to monitor critical aspects i.e. CPPs and CQAs only.
5.2.1 Protocol 3rd bullet	12	Several bullets including the below • Summaries of CQAs to be investigated and CPPs with associated limits and other non-critical attributes and parameters which will be monitored.	Suggest adding: • Sampling requirements (e.g. who, when, where, how, and justification for number of samples. • Data to be collected, purpose and assessment requirements o Rationale for the number of batches to be included o Pre-approved objective measures for evaluating between batches and within batch variability. o Statistical approaches shall be used when possible and shall be justified • Describe or reference how deviations are handled	To add clarity and align with the topics that follow in this guide Other non-critical attributes and parameters are included in the batch record.

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5.2.1	12	None – missing content within protocol	List, or reference to, critical material attributes (CMAs) for all materials to be used within the process	CQAs and CPPs are listed, but not the attributes of the materials to be used in the process.
-- ? Separate section within 5.2?	--	None – missing content	API, Raw materials and components employed in process qualification must be qualified in advance of the study(ies) or must be qualified in conjunction with the process qualification. CMAs for these materials must be identified and confirmed. A vendor qualification program and appropriate quality agreements must be in place to ensure ongoing assurance of quality post process qualification.	This could go before or after the protocol. It doesn't seem to fit within the existing subheadings but it is an important concept to ensure that all materials in used during the qualification are in a state of control.
5.2	12	You may release them (batches) after the successful completion of the Process Performance Qualification Study (providing appropriate marketing authorization has been obtained).	Clarification to be provided if all batches which are a part of the PPQ should be released only after the PPQ is successfully completed or it is permissible to release one batch at a time if it is in conformance to the PPQ acceptance criteria.	There could be instances wherein it may not be feasible to hold release of batches until the entire PPQ exercise has been successfully completed.
Section 5.2.2	13	Section 3 discusses matrix or bracketing approaches	Also discusses that bracketing may not be appropriate for "discrete steps" such as compressing different strengths. While the document states "may," we would suggest that one or two of multiple strengths can be identified as worst case with the application of science and risk-based product and process understanding and PV could focus on these.	In many cases, bracketing is appropriate across discrete steps/compressing.
Section 5.2.2	13	The number of batches to be assessed can also be reduced if product is being transferred from one facility to another	It is not clear how the assessment of number of batches linked to tech transfer of the product. Regardless of number of batches assessed at the sending site, the receiving site has to perform the assessment independently.	It is not clear how the assessment of number of batches linked to tech transfer of the product. Regardless of number of batches assessed at the sending site, the receiving site has to perform the assessment independently.

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Section 5.2.2	14	5. Concurrent validation may be acceptable in exceptional circumstances. For example, where there is a strong benefit–risk ratio for the patient.	Concurrent validation may be acceptable in exceptional circumstances. For example, products with a very small annual volume (less than 2 batches per year) like orphan drugs where there is a strong benefit–risk ratio for the patient.	Some of the new products will be launched in a relatively small quantities in next years and if concurrent validation not include a very small volume products this may create a difficulties of the patients to access of modern drugs
Section 5.2.2	14	6. Retrospective validation studies are generally not considered to be acceptable.	Please give examples or specifics of when retrospective validation studies are acceptable.	Since retrospective validation is not the preferred option for validation, providing examples/specifics removes the ambiguity of when retrospective validation is acceptable.
Section 5.2.3 Challenge plans	14	Other items to consider challenging during the process qualification study execution include: • Different API and critical excipient lots to account for lot-to-lot differences. Note: APIs and critical excipients sourced from different vendors are a potential sources of variability and require additional evaluation/testing.	Suggest adding if practical and change from different vendors to different batches (same vendor)	The assessment of different vendors for APIs or critical excipients can be addressed during Phase 1 or during the Ongoing process Verification Stage. Typically the validation of different vendors for APIs or critical excipients is validated in separate studies.
Section 5.2.3	14	5.2.3. Challenge Plans says “Manufacture qualification batches at commercial scale according to the approved manufacturing instructions under normal operating conditions”	Suggests challenging parameters that are operator adjustable during PPQ, such as compressing parameters	Challenging of parameters is part of a robust development program (PV stage 1) and should not be necessary as part of PV, unless scalability issues have not been fully addressed. Additionally, the individual operator making such a change does not impact the effect of the modified parameter. Lastly, PV batches are saleable product and in the spirit of providing the best quality possible, intentionally upsetting parameters during

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				a run could lead to waste, while the press (for example) re-achieves steady state.
5.2.3	15	None – missing content	Hold times: Hold times within a process should be challenged as part of the process qualification or should be subject to separate studies for that purpose	While there was mention of hold times earlier in the document (pg. 10), there is nothing in this section about how to incorporate them into the validation challenges.
5.2.3	15	None – missing content	Process durations: when process times may be variable due to sub-lot processing or campaigns, risk assessments should be performed to justify the approach to be pursued during the process qualification and define how it will support any extended process times in the routine phase	Processes can be longer or shorter than those included in the process qualification based on sub-lot requirements (e.g., coating pan) or campaigns (e.g., granulation), if the process qualification is to be representative of the routine phase there must be a risk assessment (at the time of qualification) that drives the approach during qualification or that drives a plan for future study within the CPV (ongoing monitoring) phase of the process.
5.2.6	15	Typo 'rages' should be 'ranges'	Correct typo	
5.2.7 Final report	16	Summarize qualification study results in a final report. The report should include (at a minimum) the following:	Suggest adding • Consider the cumulative impact of multiple deviations Include any recommended changes to correct deficiencies Suggest deleting: First bullet: refs to dev studies, equipment qualification etc	To add clarity All items in this first bullet should be in the protocol, not the report

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5.2.7	17	Not qualified – The qualification study was not successful. In such cases, you must determine the cause(s) of the failure and implement appropriate remediation actions before re-executing the process qualification study. Reprocessing or reworking of failed qualification batches to justify their release is generally not acceptable.	Please clarify if the PPQ is deemed unsuccessful if all batches which are a part of the PPQ fail to conform to acceptance criteria or a selected number of batches fail to conform to acceptance criteria. Please also specify what should be done in the event a selected number of batches fail to conform to the acceptance criteria.	There could be instances wherein a selected number of batches fail to conform to the acceptance criteria during PPQ. A clear guideline will avoid subjective handling of such situations.
5.2.7	17	Reprocessing or reworking of failed qualification batches to justify their release is generally not acceptable.	Reprocessing or reworking of failed qualification batches ~~to justify their release~~ is generally not acceptable unless the reprocessing or rework requirements and parameters are well characterized through development and are part of the market authorization. Rework processes are subject to validation to demonstrate their validity.	There are processes that are acceptable with reprocessing (usually of single unit operations), or cases where rework processes are approved for specific processes. While it is generally agreed that these should be well-characterized as to their triggers and rationales for performance, they may be acceptable. As stated, it implied that they were just being performed for the purpose of making the product comply with release criteria rather than the cases where they are a required part of the process.
5.2.8	17	Current text uses the term “continued process verification”	Suggest changing to “continuous process verification” to be consistent throughout this section	Two different terms (continued process verification, and continuous process verification) are being used interchangeably. This is confusing.
Section 5.2.8	18	5.3: - Validation Maintenance	Suggest this section be removed.	The guidance refers to Phase 3 as Validation Maintenance, this is confusing and does not align with FDA or EMA terminologies for Phase 3 which is Continued Process verification or Ongoing

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				process verification. This will be confusing for companies to implement. Any changes which are required to a process due to continuous optimization and improvement programs should be captured in the change control system and impact to the validation state assessed there.
Section 5.2.1	18	5.3.1: Ongoing process monitoring change review	Please confirm that this section is relating to "Ongoing process verification" and to state this in the heading if that is the case. State "Phase 3"	Inconsistent terminology being used in this section; Ongoing process monitoring change review, in heading and ongoing verification in bullet 6
Section 5.3.1	18	5.3.1: Ongoing process monitoring change review	Suggest to clarify if section applies to new products only or also products with a long history.	Clarification requested.
5.3.2	19	5.3.2: change review	The criteria for revalidation should be included.	Changes in sources of raw material are common in the industry. The new source could supply raw material of the same physical property as the one presently being used. Handling such situations is again subject to individual interpretations.
6.2 Facility, equipment and utility qualification	20	Section 6.2 states the qualification requirements for FE&U	Verification is not listed as alternative to qualification. Is Health Canada open to verification as an alternative to qualification following ASTM E 2500, or similar?	Clarification
6.3 Computer system	22	• The ongoing performance of the system is monitored in accordance with a procedure.	Suggest clarifying the intent of this statement	We are not sure what is meant by this statement for Computer Systems.

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validation item 2				
6.4.1	22	None – missing content	As with other forms of qualification, sampling plans for assessing package integrity must be statistically sound and must be representative of the known sources of variation within the process; methods used to ensure package integrity must be validated for their use; as with other process qualification, packaging qualification batches should be enrolled in stability.	While these requirements could be inferred from other sections of the document (p. 12, 15, 19), the other sections discussed these elements from a chemical stand point and not from a physical test methodology requirement as would be applicable to packaging components.
Blend uniformity assessment	25	1. Blend uniformity assessment: Obtain samples from the blender at the completion of the mixing process, to ensure the blend is well mixed and that no difference exists between locations in a blend that could adversely product quality	Suggest changing “that no difference exists between locations” to “no significant variability is observed between locations”.	It is not practical to require no difference in blend uniformity results for between locations.
Appendix A Box	25	Direct Compression may not be appropriate for low dose	Would like to see this statement removed	A highly automated direct compression process for a low dose product, such as continuous manufacturing may actually lead to superior product.
Appendix A	25	Blend uniformity assessment: …that could adversely product quality.	Add the word “affect” between adversely and product.	To correct sentence.
Appendix B	30		Include definition for “Ongoing process verification”.	There is no definition included for ‘Ongoing process verification.