Connecting a World of Pharmaceutical Knowledge

30 September 2011

Scientific Liaison
(PS05) Packaging and Storage Expert Committee
US Pharmacopeia
12601 Twinbrook Pkwy
Rockville MD 20852-1790

Re: Proposed revisions to USP General Chapter <1079> Good Storage and Distribution Practices For Drug Products

ISPE appreciates the opportunity to provide comments on the proposed revisions to USP General Chapter <1079> Good Storage and Distribution Practices for Drug Products. Our comments are summarized in the accompanying table. We hope you find these useful. We would be happy to provide any additional information or explanation, if required,

Please let me know if you have any questions.

Yours Sincerely,

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President/CEO
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ENGINEERING PHARMACEUTICAL INNOVATION

Regulatory Comment Form

Proposed Regulation/Guidance Document: USP General Chapter<1079> Good Storage and Distribution Practices for Drug Products

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SECTION	CURRENT WORDING	PROPOSED CHANGE	RATIONALE
DEFINITIONS Environmental Management Program	A program that covers temperature, humidity, light and/or other environmental controls that require consideration in the storage and distribution of product throughout the lifecycle.	As written the definition would apply to an environmental monitoring program, rather than a management program	The management program would ensure identification of quality critical environmental aspects for the product and ensure that adequate processes to maintain that environment were in place.

SCOPE	The scope includes clinical trial materials products, but much of the guidance within the document is geared towards commercial products.	Include a section specific to PII & PIII clinical trial materials.	A lot of the document speaks to practices that are very relevant for commercial drug products but, may not be applicable to clinical trial activity. For example temperature mapping of freight trucks etc would not be value-added based on typical small parcel transport typically used in clinical trial applications. It would be value-added to have a section specifically speaking to clinical trial materials, as they do have unique challenges when compared to commercial goods. We recognize Phase I drug is specifically excluded, but feel there is a gap regarding later phase clinical trial materials

SCOPE	Scope includes Brokers, Importers, and Exporters but there is no mention of best practices with respect to preparing for customs activities	Include insight/guidance on what distributors can do to minimize loss as products clear customs.	Customs practices, as they relate to freight handling, can be poorly understood. Inclusion of discussion on how freight is typically handled as it clears customs may be helpful to distributors in that they can better prepare for extended delays etc. There is more variability in clinical trials based on the broad number of countries that can be included in later phases. Commercial transit lanes tend to be better understood based on their repetitive nature.
BACKGROUND INFORMATION	Storage and distribution processes involve a complex movement of product around the world, differences in documentation....	Storage and distribution processes "*may"* involve a complex movement of product around the world, differences in documentation……	Suggest adding *"may*"; not all processes are complex.
RESPONSIBILITIES	No comments		

LABELING CONSIDERATIONS FOR DRUG PRODUCTS	The reference to the use of other storage conditions is vague and open to interpretation.	Suggest revising to *"should provide the receiver with instructions for the correct handling of the product"…..*	Revision to clarify the requirement.
	When a drug product's storage conditions are not readily available, use the storage conditions described in "*General Notices and Requirements"* or the applicable monograph.	Contacting the manufacturer to determine the requirements would be a more robust approach.	The reference to the use of other storage conditions is vague and open to interpretation. Revision to clarify the requirement.
QUALITY MANAGEMENT SYSTEM			

Good documentation practices	The following elements should be included: (1) how products are handled when equipment malfunctions or when there are delays in distribution due to customs hold or temperature deviations….	May be better written as*" how products are handled when equipment malfunctions or when there are temperature deviations e.g. due to delays in distribution due to customs…."*	Revision to improve clarity.
	The QMS should require monitoring of processes to demonstrate that a state of control has been maintained, where the set of controls……	Suggest revising the wording as shown here: The QMS should require monitoring of processes to demonstrate that a state of control *"is being"* maintained, where the set of controls……	Revision to improve clarity.
Storage management system	No comments		
Storage Locations and Processes	No comments		

Storage in Buildings and Facilities	These facilities should be adequate to prevent overcrowding, which can lead to contamination.	This sentence Is based on some tenuous assumptions. Over- crowding should be defined, and the supposition removed. *"It is assumed that an overcrowded facility would not have adequate space for cleaning, pest control, safe and efficient operation"* is more descriptive of specific concerns.	Revision to improve clarity.
Receiving and Transferring Drug Products	No comments		
Refrigerators and Freezers	Typically, a refrigeration unit specification would be set to 5°, with an accuracy of ±3, to store products labeled 2°-8°.	The sentence assumes that the temperature will be centered around the equipment set point. This may not be the case, and is not relevant here. The unit should maintain conditions between 2° and 8°.	Technical correction

	Units should store items in a manner allowing sufficient space to permit proper air flow	Change sentence to read: "*Part of the qualification process is to ensure that with the defined storage conditions, the specified conditions are maintained"*.	Clarify the requirement. This is less ambiguous; i.e. what is "proper" airflow?
DISTRIBUTION MANAGEMENT SYSTEM	No comments		
Packaging for the Distribution and Transportation Processes	Package performance testing should be documented as part of a manufacturer's robust QMS.	"Robust" QMS should just be QMS, unless robust is defined.	Revision to clarify the requirement.
	Those tests include the following: the American Society for Testing and Materials (ASTM), ……"	Change sentence to read: *"Organizations with standard test methods include…"*	Revision to improve clarity.

	The shipping container used for the distribution of product should be selected to ensure that product quality is maintained and to protect the contents from the rigors of distribution, including environmental or physical damage.	Should the requirement defined here be more flexible, e.g. by adding: *"The transport container for drug products should be qualified "or monitored" on the basis of the labeled conditions of the product"* to better align with the following section?	Revision to improve clarity.
	All drug products have storage requirements that may contain specific controls, as well as anticipated environmental conditions (consider seasonal temperature differences, transportation between hemispheres, and the modes of transport).	May be more representative if revised to: "*Consider seasonal temperature variations, the impact of the modes of transport used and route on the external conditions."*	Revision to improve clarity.

	The type, size, location, and amount of refrigerant required to protect the product should be based on documented studies of specific distribution environments, including domestic and international lanes, modes of transport, duration, temperature, and other	Sentence uses “refrigerant” in an unusual context. Should this be more generic, for example: *” capacity of the mechanism used to maintain the specified conditions”*	Revision to improve clarity.

Validation and Thermal Performance Qualification	Storage facilities themselves, unless thermostatically controlled, cannot be validated because of their unpredictability and the influence of external temperature; however, they can be qualified via a mapping process. The generator back-up power supply should be validated.	The paragraph is not technically correct. The thermal performance of a facility can be predicted using standard software to a reasonable degree of accuracy, using historical weather data - with temperature mapping used to confirm the results. Monitoring is then used to confirm that a facility maintains conditions, and provides a record.	Technical correction.
		General statement: Where necessary, the provision of appropriate utility systems should be considered, but it would be clearer to state that HVAC systems may be required to maintain specified conditions.	Revision to improve clarity.

	The generator back-up power supply should be validated.	It would be very unusual and unnecessary to “validate” a generator. You would not validate the utility power supply system. These systems are commissioned, tested and maintained following good engineering practices.	Technical correction.
		General statement: The references in this section should also include ASTM E2500 and the relevant ISPE guides.	The risk based approach requires verification of the correct installation and operation confirmed by an appropriate SME.

ENVIRONMENTAL MANAGEMENT SYSTEM	Guidance document focuses on vehicle and container temperature mapping. Agree that this is best practice for commercial goods.	Consider a section specifically addressing late phase (e.g.PII & III) clinical trial drugs.	In many cases, it may not viable to perform exhaustive temperature mapping of container/vehicle in a clinical trial environment. The lifecycle of the drug may be short; there tends to be a wide array of transit lanes with variable number of shipments occurring in each (some small some large). Additionally, packaging & dosage presentations may change as the product develops, which can impact previous mapping activities. Consider a section specifically speaking to clinical trial materials, where activities such as carrier service selection, data loggers, active cooling devices, may be more viable options given the uncertainly of a research product's life cycle and the rapid on & off boarding of participating countries (within a clinical trial).

Temperature Monitoring	Temperatures should be controlled and tracked using a monitoring system, and the monitoring devices used should be included in a preventive maintenance program.	Suggest revising to clarify the intent: *"Where appropriate, critical conditions should be maintained by an HVAC system. The monitoring system should confirm that areas used for product storage are maintained within the specified limits."*	Revision to improve clarity. The terminology used is not very consistent. Typically the temperature control system (HVAC) is separate to the monitoring system. By "preventative maintenance program", the implication is a calibration program?
	Temperature monitor(s) should be used with every distribution process unless some other process has been put in place to ensure adequate handling (validated containers).	The sentence is not clear. Changing to the suggested text below would help: Temperature monitor(s) should be used with every distribution process unless some other process has been put in place to ensure "*specified temperatures are maintained"* (validated containers).	Revision to improve clarity.

		General statement: Definition of the load would also define the airflow patterns, so including a mention of airflow implies that additional testing is required. This is not typically done, as the temperature mapping alone will confirm the storage conditions, considering all potential variables, to meet the specifications.	Revision to improve clarity.

Temperature Mapping	The recording of temperatures during the thermal mapping of a warehouse or cold room should be sufficient in timeframe to capture workflow variation that may impact air flow and the resulting temperature fluctuation (i.e., a period of two weeks is recommended for data collection enabling the capture of two week/weekend workflow cycles).	What is the justification for a two week mapping period?	Revision to improve clarity. Activities are generally cycles: Operation with no access (overnight / weekends); Loading; Unloading. The verification testing should encompass these conditions. Ongoing monitoring of the unit should confirm that it is operating to maintain the specified conditions, regardless of changes in the usage. Even large systems reach stable conditions in a short time.

		General statement: The wording of this section is heavily focused on dedicated transport vehicles. Many shipments of clinical trial materials are small packages using standard courier services to provide “just-in-time” delivery for individual patients. As such, non-dedicated containers and vehicles are used; the proposed text would point toward the need for other means of control to be put in place. This is not realistic or proportionate to the risk. It should be clear that exemptions based on short shipment times may be justifiable.	

		General statement: The examples shown in this section are of a trailer, not a facility. Appropriate examples should be used. The specific use of IQ and OQ does not align with the terminology used in ASTM E2500.	Revision to improve clarity.
		General statement: The use of trailers meeting a specification is not mentioned in this section, e.g., ATP provides an "Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment" to be used for such carriage. <http://www.unece.org/trans/main/wp11/atp.html>	Missing technical reference.

	Further, temperature data loggers should be calibrated to an accuracy specification of ±0.5°	Does the note regarding the accuracy of the instruments used to map imply that the acceptable range stated in the definitions allows for that accuracy? Although we understand that they are the "true" temperature limits.	Revision to improve clarity.
Excursions	No comments		
MKT Calculation	No comments		
MKT During Storage and Distribution	No comments		

RISK MANAGEMENT SYSTEM		General statement: This section should focus on the basics of a risk assessment process (i.e., identification, evaluation, and action plan). The examples given are too specific and cover topics that are not mature (i.e., risk of vibration that can cause aggregation).	
CONCLUSION	No comments		
ADDITIONAL COMMENTS	It is important to have the same standard nationally within the U.S., as well as internationally, in order that global companies can follow a single, consistent set of guidelines. Therefore, we strongly encourage USP to consider alignment with the emerging guidelines from the EU and WHO.		