Guidance 126: Establishing Re-evaluation Intervals for API Intermediates

Appendix I

(Determination of a microbial proliferation *Risk Band* to help propose a reevaluation interval for wet intermediates)

Severity Factors for Microbial Proliferation (Risk Category One)

Factor	Description
1	Solid Oral Dosage, Powder for Oral Suspension, nonaqueous liquid Oral Dosage Product, nonaqueous liquid or semi-solid Topical Product
2	Aqueous Liquid Oral Dosage products, Aqueous liquid or semi-solid Topical Products, Otic Products, Ophthalmic Products, and Inhalant Products
3	Sterile Injectable Products

Probability Factors for Microbial Proliferation (Risk Category Two)

Factor	Description
1	Characteristics of the intermediate are not favorable for microbial proliferation (See Appendix II) - **no proliferation of bioload**
8*	Characteristics of the intermediate are favorable for microbial proliferation (See Appendix II **possible proliferation of bioload**

*Probability reduction considerations affecting intermediates stored in conditions favorable for microbial proliferation that can be subtracted from the factor "8" to lower the probability factor.

3	Intermediates stored at conditions (eg. refrigerated) not conducive to microbial proliferation - **bioload stabilized**
2	Preceding and/or succeeding processing steps relative to the storage of intermediates are hostile (i.e. high temperature, high/low pH and/or high solvent content) to microbial viability - **bioload reduced before or after storage**
1	Intermediates packaged using a closed system or in a controlled environment – **reduced opportunity for addition to bioload**

Example: The intermediate is stored wet with water but the manufacturing process before storage and/or after storage is hostile and packaging is performed in a closed system. Subtract 3 (2 + 1) from the factor "8" to get an adjusted probability factor of 5.

Appendix I (continued)

Severity Factor x Risk Factor = Risk Band and Proposed Risk Based Reevaluation Interval

Probability →				
	8	8-R	16-R	24-R
	7	7-R	14-R	21-R
	6	6-O	12-O	18-O
	5	5-Y	10-O	15-O
	4	4-Y	8-Y	12-Y
	3	3-G	6-Y	9-Y
	2	2-G	4-G	6-G
	1	1-G	2-G	3-G
		1	2	3
		Severity →		

Risk Band	Proposed Reevaluation Interval
G-Green	12 Months
Y-Yellow	3 Months
O-Orange	30 Days
R-Red	72 Hours

Example: Risk Based Reevaluation Interval

	Severity Factor
• Solid Oral Dosage	1

	Probability Factor
• 100% water wet	8
• Hostile before storage	-2
• Packaged into FIBC-closed system	-1

Adjusted Probability Factor	**5**

Risk Band (1 x 5) **5 (Y-Yellow)**

Proposed reevaluation interval due to microbiology is----------3 Months

Appendix II [3]

(The table below can be used to determine whether or not the attributes of an isolated intermediate stored wet are favorable for microbiological proliferation.)

Starting material or intermediate was derived synthetically or derived from plant, animal, fermentation, or bioconversion and has been through an extraction into a water immiscible solvent.		Starting material or intermediate was derived from plant, animal, fermentation, or bioconversion and has not been through an extraction into a water immiscible solvent.	
Attribute of wet intermediate	**Yes/No**	**Attribute of wet intermediate**	**Yes/No**
Water activity (a_w) value is <0.60 [2]		Water activity (a_w) value is <0.60 [2]	
pH < 3		pH < 2	
pH > 10		pH > 10	
Methanol > 40% relative to water		Methanol > 50% relative to water	
Other Alcohols > 20% relative to water		Other Alcohols > 40% relative to water	
THF > 30% relative to water		THF > 30% relative to water	
Acetone > 30% relative to water		Acetone > 30% relative to water	
Wet with a water immiscible solvent		Wet with a water immiscible solvent	

If the answer is **Yes** for any of the attributes above then the wet intermediate can be considered to be held under conditions unfavorable for microbiological proliferation.

If the answer is **No** for **all** the attributes above, then the wet intermediate should be considered to be held under conditions favorable for microbiological proliferation.

Appendix III

Ways to perform intermediate hold time studies to test the impact of any potential chemical degradation on the final API.

Retrospective Analysis – Information necessary to support reevaluation intervals between steps can be gathered through historical data which may include but is not limited to:

- Completed & reviewed production batch records
- Storage information from Material Management Systems
- Records of approved Validation batches
- Data from process development
- Stability data, where available (sold intermediates)
- Site incident investigation database.

Information taken from the above records may include analytical results, processing issues, storage conditions and maximum length of storage time.

It is recommended that a report be prepared from this data with a conclusion statement regarding the longest the material could be stored without problems occurring with subsequent processing steps or with the final API.

Prospective Analysis– Establishing hold time limits for API Intermediates on a real time basis is also acceptable. A protocol approved by the Site Quality Authority can be written to specifying the study duration and conditions. The hold time is considered verified and acceptable if the protocol requirements are met at the end of the study. The study protocol may include the following considerations:

- The number of containers to be evaluated – Enough material should be held to process a reduced batch size all the way to the final API.
- The warehouse location and conditions should be consistent with regular production.
- The type of testing to be performed – to include material characteristics which could have an impact on product quality. Minimum testing would be final API tests.
- The approved in-process or release test methods to be used in the study
- The frequency/interval of testing – a minimum of time-zero and end-of-study testing is recommended. However, testing at intermediate time points may be performed to assure identification of trends and anomalies
- The number of lots to use for the study (Note: As few as one lot may be used for a hold time study)
- The acceptance criteria to be met to demonstrate the hold time is acceptable.

Appendix IV

How to perform a microbiological proliferation study on wet intermediates

A protocol approved by the Site Quality Authority can be written to specify the study duration and conditions. The hold time is considered verified and acceptable if the protocol requirements are met at the end of the study. The study protocol may include the following considerations:

- The number of containers to be evaluated – Store at least one standard container from each of three batches of wet intermediate.
- The warehouse location and conditions should be consistent with regular production.
- The type of testing to be performed – Perform the USP General test <61> "Microbiological Examination of nonsterile products: Microbial Enumeration Test".
- The frequency/interval of testing – a minimum of time-zero and end-of-study testing is recommended. However, testing at intermediate time points may be performed to assure identification of trends and anomalies
- The acceptance criteria for the study is based on the closeness of the intermediate step to the final API step, the total viable count at time zero, and end use of the API.