Manual 045

Appendix

Appendix 1

Protocols

Protocols should be prepared at all stages so that it is clear what should be done. The level of details will increase during development.

Example stability protocols are provided here for guidance.

Development protocols

Table 1 Example of a Stability Protocol for Packed Investigational Medicinal Products

Months	25°C/60%RH	30°C/65%RH	40°C/75%RH	50°C	Photostability
1	O		O	O	O[a]
3	T	O	T	O	
6	T	O	T		
9	O	O	O[c]		
12	T	O			
18	O	O			
24	T	O			
etc[b]					

T = testing
O = Optional
References should be stored at 5°C
[a] = Actual time depends on light intensity, maximum exposure detailed in ICH guideline Q1B
[b] = Longer storage time optional
[c] = May be required to support clinical studies conducted in Zone IV countries.

For sensitive formulations (e.g. solutions or suspensions) long term condition in the freezer or refrigerator may be necessary. For these studies refrigerator or 25°C/60%RH respectively are accelerated conditions.

Formal protocols

Drug substances are typically manufactured, shipped and stored in Zone I/II territories for the manufacture of drug products. The long term formal stability condition for drug substances should therefore be 25°C/60%RH (±2°C, ±5%RH) or 5°C (±3°C) with the appropriate accelerated conditions selected according to current ICH guidelines Q1A.

For a stable drug product, if the following stability protocol is to be followed the Zone I/II regulatory authority should be consulted at the end of Phase II in order to gain approval on the use of 30°C/75%RH as the long term condition prior to commencing the formal stability studies.

Table 2 Example of a Stability Protocol for Worldwide Marketing of a Stable Product

Months	25°C/60%RH[a]	30°C/65%RH[a]	30°C/75%RH[a]	40°C/75%RH[a]	50°C[b]	Photostability[b]
1	-	-		-	O	T[c]
3	O	O	T[d]	T	T	
6	O	O	T	T		
9	O	O	T			
12	O	O	T			
18	O		T			
24	O		T			
36	O		T			

T = testing
O = Optional
References should be stored at 5°C
[a] = 3 batches
[b] = One batch only
[c] = Actual time depends on light intensity, maximum exposure detailed in ICH guideline Q1B
[d] = If applicable, one batch stored open to support pharmacy dosing regimes

Table 3 **Example of a Stability Protocol for Worldwide Marketing of a Less Stable Drug Product**

Months	25°C/60%RH[ae]	30°C/65%RH[af]	40°C/75%RH[ae]	50°C[b]	Photostability[b]
1	-		-	O	T[c]
3	T[d]	O	T	O	
6	T	O	T		
9	T	O			
12	T	O			
18	T				
24	T				
36	T				

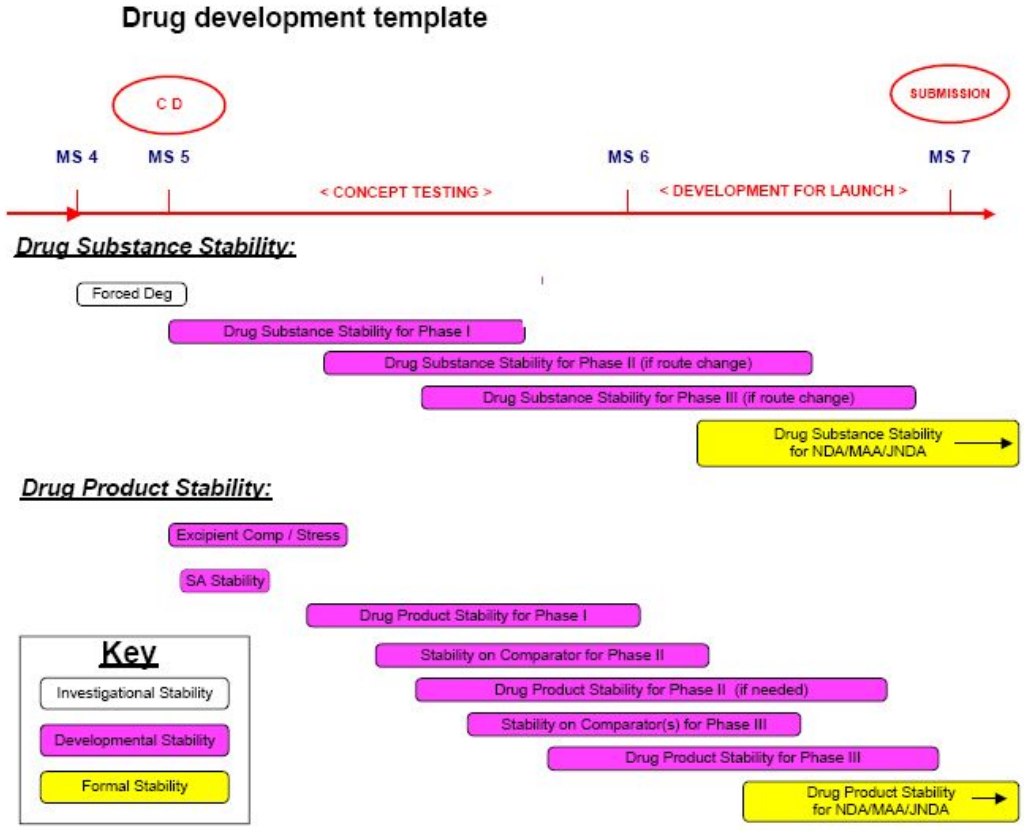
T = testing
O = Optional
[a] = 3 batches
[b] = One batch only
[c] = Actual time depends on light intensity, maximum exposure detailed in ICH guideline Q1B
[d] = One batch stored open to support pharmacy dosing regimes
[e] = Where a more protective pack has been developed to protect a moisture sensitive drug product for Zone IV markets, conduct testing at the long term condition of 30°C/75%RH and accelerated testing at 40°C/75%RH, see Table 2.
[f] = ICH Intermediate condition if failure at 40°C/75%RH should occur

Allocation of re-test period/shelf life

Table 4 **Allocation of Re-test period/Shelf life for Stable Non-clinical and Investigational Material**

Storage condition	Extrapolation factor	Time point (months)	Maximum extrapolated re-test period / shelf life	Example
Thermal stressed (50°C)	x 6	a	6 * a	Where a = 1 month max shelf life = 6 months
Accelerated (40°C/75%RH)	x 4	a	4 * a	Where a = 6 months max shelf life = 24 months
Long term (25°C/60%RH) or Intermediate (30°C/65%RH) **AND** accelerated (40°C/75%RH)	x 2	a	2 * a (≤18 months data) a + 12 (>18 months data)	Where a = 18 months max shelf life = 36 months Where a = 24 months max shelf life = 36 months

Appendix 3


Drug development template
CD
SUBMISSION
MS 4
MS 5
MS 6
MS 7
< CONCEPT TESTING >
< DEVELOPMENT FOR LAUNCH >
Drug Substance Stability:
Forced Deg
Drug Substance Stability for Phase I
Drug Substance Stability for Phase II (if route change)
Drug Substance Stability for Phase III (if route change)
Drug Substance Stability for NDA/MAA/JNDA
Drug Product Stability:
Excipient Comp / Stress
SA Stability
Drug Product Stability for Phase I
Stability on Comparator for Phase II
Drug Product Stability for Phase II (if needed)
Stability on Comparator(s) for Phase III
Drug Product Stability for Phase III
Drug Product Stability for NDA/MAA/JNDA
Key
Investigational Stability
Developmental Stability
Formal Stability

Appendix 4

Recommended testing conditions for drug substances and drug products

Table 5 **Recommended testing conditions for drug substances and drug products**

Condition °C/%RH[1]	Comment
Drug substances and products, general case[2]	
25/60	Long term condition (Climatic zones I and II)
and/or	
30/75	Long term condition (Climatic zones III and IV). Consultation with regulatory authority required if used as the long term condition in zones I and II.
30/65	Intermediate condition (Climatic zones I and II), up to 12 months, for use if significant change at 40/75,
40/75	Accelerated condition, up to 6 months
50/Ambient	Stressed condition to cover extremely hot and dry conditions
Drug substances or products intended for storage in a refrigerator	
5/Ambient	Long term condition
25/60	Accelerated condition, up to 6 months
Drug substances or products intended for storage in a freezer	
-20/Ambient	Long term condition
Aqueous-based Drug Products packed in semi-permeable containers[3]	
25/60 (alt 25/40)	Long term condition (Climatic zones I and II). Water loss evaluation at 25/40 according to ICH Q1A
and/or	
30/65 or 30/75 (alt 30/35)	Long term condition (Climatic zones III and IV) Alternative to long-term storage condition for climatic zones I and II for stable products. Water loss evaluation according to ICH Q1F
30/65	Intermediate condition, up to 12 months, for use if significant change at 40/75, and if 25/60) (alt 25/40) is the long-term condition
40/75 (alt	Accelerated condition, up to 6 months

Table 5 **Recommended testing conditions for drug substances and drug products**

Condition °C/%RH[1]	Comment
40/NMT25)	Evaluation of significant water loss at not more than 25% RH according to ICH Q1A
Inhalation Products	
25/60	Long term condition (Climatic zones I and II)
and/or	
30/75	Long term condition (Climatic zones III and IV)
25/75	Additional intermediate condition for US only, up to 6 months for use if significant change at 40/75 for any of the parameters delivered dose or fine particle size distribution
25/75	Additional condition for products using a protective, secondary package (e.g. foil over wrap). Storage in secondary package up to 1/3 of expiration dating period and without secondary pack for a period corresponding to the in-use shelf life.
30/65	Intermediate condition, up to 12 months, for use if significant change at 40/75, and if 25/60 is the long term condition (US and others)
40/75	Accelerated condition, up to 6 months

Note 1: Temperatures greater than 15°C should be controlled within the range ±2°C, for 5°C ±3°C and -20°C ± 5°C. Relative humidity should be controlled within the range ±5%.
Note 2: Stability studies on drug products in impermeable containers can be conducted at any controlled or ambient humidity condition
Note 3: Water loss rates should be determined by measuring weight loss, at least once for a specific semi-permeable pack at different conditions e.g. 25, 30 and 40°C with relatively low humidity. General case conditions can be used for stability studies once a linear water loss over time has been demonstrated. The effect of water loss should always be considered when evaluating stability data.