Consumer Healthcare Products Association

In-use Product Stability Testing for OTC products – Advisory Document

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Introduction

The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, shelf life for the drug product and recommended storage conditions. In cases where in-use testing is required then this best practice provides examples of how to conduct the testing. The purpose of an ***in-use stability study*** is to establish the period of time during which multi-dose products can be safely and effectively used after opening and still comply with critical quality attributes (shelf-life specifications). In-use stability is generally applicable to aqueous preparations; however, some regulatory agencies are now requesting in-use stability data for all other dosage forms, e.g., topical creams/ointments, solid dose tablets/capsules in multi-dose packaging.

The following are regulatory documents that reference in-use stability studies:

- *Note for Guidance on In-Use Stability Testing of Human Medicinal Products* Committee for Proprietary Medicinal Products CPMP/QWP/2934/99 (2001)

- *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* WHO (2009) Annex 2

- *Agência Nacional de Vigilância Sanitária (ANVISA),* National Health Surveillance Agency Brazil RCD 71/2009 (2009)

- Mexico Guideline NOM-073-SSA1-2015, Drug substances, Medicines and Herbal Remedies Stability.

The above-mentioned regulatory documents are not comprehensive but serve only to provide general guidance on establishing in-use stability protocol design and testing, where expected. Therefore, with input from members of the Consumer Healthcare Products Association (CHPA), the authors have developed this advisory document as a reference for the OTC industry to provide additional details and risk-based rationale for establishing appropriate in-use stability study designs, testing criteria and interpretation of the in-use stability data.

Scope of the In-Use Stability Advisory Document

- The purpose of in-use stability testing is to establish - where applicable - a period of time during which a multidose product can be used while retaining quality within an accepted specification once the container is opened.
- This advisory document does not cover products that are classified as single dose (i.e. blisters or sachets, etc.).

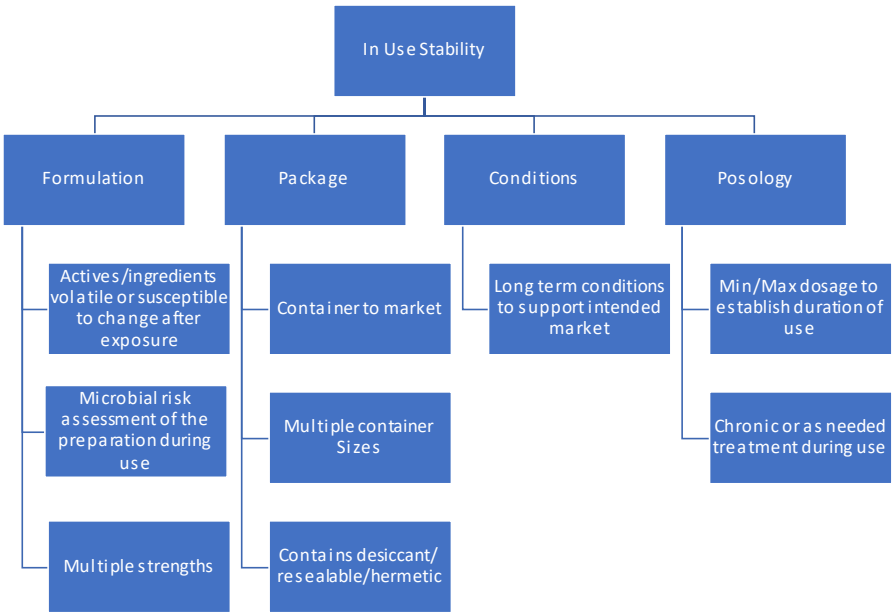
- This advisory document does not address circumstances where the label indicates the product should be consumed or used immediately (i.e., reconstituted).

Principles

I. Considerations for designing an in-use stability study

Parameters to be considered in the design of an in-use study are presented in Figure 1.

Figure 1. Considerations for Design of an in-use stability study



- If a product is marketed in multiple container sizes, the study should be applied to the worst-case size or apply a bracketing approach. Typically, the largest container size is considered the worst case because of the greatest headspace, the number of manipulations and the duration of use. Different packaging sizes should consider different durations of the in- use stability study design.
- If the container closure system is resealable/hermetic or contains a desiccant, then take into consideration whether that should be part of the in-use stability design.
- Microbial risk assessment of the preparation during an in-use stability study should be performed to determine the need for assignment of specific testing parameters and acceptance criteria. Intrinsic microbiological robustness of the multi-dose preparation should be assessed that integrates:
    - Understanding of the physical form integrity of the preparation (e.g., phase separation of emulsions)
    - Integrity of the preservative system or anti-microbial challenge test (where appropriate)

- Other associated physical-chemical hurdles to suppress microbial growth.
- Recommended consumer use per label instructions. In addition, projected repurchase information may be beneficial to consider when designing the in-use stability study.

- The intended purpose of the formulation should be considered i.e. if the product is:

  'Chronic' where the consumer would be expected to fully consume/use the product consistently/routinely in alignment with the maximum daily dosage of the product label.

  'As needed' where the consumer would be expected to consume/use the product periodically throughout the shelf life of the product.

II. Design

An in-use stability protocol is needed to describe the procedures and acceptance criteria for the determination of the in-use shelf-life period. The design should include:

1. Selection of Batches

- According to regulatory guidelines (EU and WHO), a minimum of two batches should be used for the in-use stability study, one tested on a fresh batch and the other batch tested towards the end of shelf life. If two such batches are not available, then a single batch can be used where a portion of the samples are split for a fresh and at expiry in-use testing. Some agencies may require three batches based on local agency requirements (i.e. Brazil).
- In-use stability is typically conducted during product development pre-launch and these batches should be representative of commercial products, typically pilot scale or larger as per ICH Q1A. A control (un-opened) sample may be included if the in-use stability study is not concurrently tested with the ICH stability studies and/or if historical stability data does not exist.

2. Test Storage Conditions

Samples should be placed on stability to support the climatic zone where product is intended to be marketed:

- For markets in Climate Zones, I and II: 25°C/60% RH
- For markets in Climate Zones III, IVa and -IVb: 30°C/65% RH or 30C/75% RH

Note: Aqueous based products packaged in semipermeable containers should consider low humidity conditions or apply the ICH Q1A alternative reference calculation for water loss.

Also, if marketing globally, consider a storage condition that supports all climatic zones (I-IVb)

3. Test Parameters

Based on the product category, dosage form, and product usage; the types of tests listed in Table 1 and additional stability indicating attributes should be considered. The need for conducting chemical, physical and/or microbiological testing of the product should be established using a risk-based approach rather than adoption of all testing that has previously been assigned to determine the shelf-life of the unopened product. Note that in many cases, scientific technical justification may also be necessary to support testing that will not be assigned for in-use stability testing but is assigned as a long-term stability commitment.

Table 1: Examples of Test Parameters to Consider

Chemical Testing Considerations	Physical Testing Considerations	Microbiological Testing Considerations[1]
Assay (active ingredient) Assay for preservative pH Related substances	Physical attributes (such as appearance, viscosity and if applicable, aroma) Particle size Package observations and functionality	Microbial Limits Antimicrobial Effectiveness Test (AET) Water activity

[1]Refer to Appendix I for additional considerations in the design of tests to confirm microbial integrity of the preparation is sufficiently maintained during in-use period.

4. In-use Sampling

- Design of the in-use study should simulate as closely as possible the use of the product by the consumer as indicated on the product label.
- Based on the posology for the product, a short and/or long duration in-use stability study should be conducted. This study is based on the parameters noted in Section I (chronic or as needed) with intended purpose of product and prescribed posology.
- In-use sampling plans, at minimum should be at initial time point and end points. Intervals comparable to those simulated during use and testing may be performed at intermediate time points.

Note: An alternative approach to the in-use sampling is to dispense 50% of product at an initial time point, then test at the scheduled intervals. This approach does not include additional

dispensing at scheduled intervals, but the product/pack can still be manipulated to mimic usage (e.g., inverting, shaking, opening).

- As justified, removal or dispensing should be in a controlled area and samples returned to the stability chambers soon as practically possible.
- Appendix II and III provides examples of in-use stability protocols. Please note, the in-use designs are examples for guidance only.

III. Evaluation of in-use stability data:

The available data should be evaluated against the stability data for pivotal/registration or if applicable against a control (un-opened) to evaluate if the product is showing any obvious trends that could potentially be attributed to the product being handled and or exposed to air after opening. Results should be evaluated for any significant changes as defined in the ICH. If the in-use stability data show adverse trends or significant changes, then an "in-use shelf life after opening" should be applied to the product label.

IV. Justification for not conducting in-use stability.

In-use stability testing may not be necessary under all circumstances. In determining the scope of testing, companies should consider microbiological robustness, API stability, and protective properties of the container closure system. In-use stability testing may not be needed if:

1. There is a strong chemical and microbiological understanding of the formulation (actives and ingredients) in which the formulation withstands exposure upon opening based on supportive literature (i.e., the formulation is not sensitive to environmental conditions outside of its primary packaging).
2. The product is expected to be consumed within a short period of time that does not present chemical and microbiological concerns.
3. The container closure system maintains the integrity of the system is resealable/hermetic and does not allow moisture and oxygen ingress/egress.
4. In-use stability data from other similar formulations is available for comparison.

Consult with the relevant regulatory agencies to ensure a thorough risk assessment is conducted, if applicable.

Appendix I: Microbial Risk-Based Considerations

Limited external regulatory guidance is available pertaining to the microbial quality of multi-dose preparations being sufficiently maintained during in-use periods. For example, consideration of microbiological examination testing for total viable count is noted in guidance provided by the European Agency for the Evaluation of Medicinal Products but lacks guidance for assignment of specific

acceptance criteria. The assignment of microbiological examination testing and criteria (e.g., limits tests and other USP tests for specified microorganisms) do not represent appropriate parameters for in-use stability testing as these tests and criteria are implemented as part of GMP requirements such as U.S. 21CFR211.113(a) and 211.165(b) to help ensure appropriate microbial quality of unopened product is met at manufacture release. Rather, considerations of other testing indicators such as preservative content assay would represent a more meaningful test option in which specific success criteria can be reapplied from other ICH pre- market (pivotal) stability studies. Other published guidance is consistent with this approach[1].

Proposed Framework for Assignment of Appropriate Testing:

The overall intent of establishing product in-use stability periods is to ensure that multi-dose products remain efficacious and will pose minimal safety risk to the end user during the in-use period (i.e., once product is opened). This includes assurance that microbial quality is maintained during such periods. Microbial quality is defined primarily as finished product preparations that would not support proliferation of microbial contaminants, if introduced during in-use periods under typical or simulated consumer practices. Using a microbial risk-based approach, the testing options listed in Table 2 can be considered for demonstrating microbial quality of the product is maintained during the in-use stability period.

Table 2

Test Parameter (Example)	Proposed Assigned Testing (Example)	Proposed Acceptance Criteria	Basis
Chemical[a] attribute(s) that provide a microbial hurdle (pH, alcohols, surfactants)	Chemical attribute(s) of aqueous, non-preserved preparations (e.g., ≥20% v/v alcohol) that enables meeting appropriate USP/EP AET criteria	Assign stability Lower Specification Limit (LSL) of the chemical attribute(s), as established from ICHQ1A pre-market stability	Confirms integrity of the chemical attribute(s) during the in-use period
Preservative content Assay	Preservative system in aqueous preparations designed to meet appropriate USP/EP AET criteria	Assign stability LSL for each preservative ingredient, as established from ICH pre-market stability	Confirms integrity of the preservative content level(s) during the in-use period
Physical[a] attribute that provides a microbial hurdle (water activity[b])	Stable low water activities (e.g., <0.70) for non-aqueous preparations	Assign water activity as a monitoring requirement only to assess trending during in-use (e.g., no increase above 0.70)	Confirms integrity of the physical attribute during the in-use period

[1] In-Use Stability Testing: What Data Are required And When? S. Sutton, B. Matthews, and D. Dunn. The Regulatory Affairs Journal. October 1998.

Antimicrobial Effectiveness Test (AET)	Aqueous preparations having marginal preservative effectiveness in ICHQ1A pre-market stability or in which no LSL for preservative or other chemical attribute has yet been established	Meets acceptance criteria corresponding to the appropriate USP or EP compendial product category	Confirms antimicrobial effectiveness of the preservative system during the in-use period
Microbiological limits (i.e., Total Aerobic Microbial Count=TAMC)	Assigning TAMC test only may be considered for marginally hostile aqueous preparations when placed in clinical-based in-use studies	Observed increase in TAMC (cfu/g or ml) above T=0 baseline counts not to exceed 1 Log during duration of in-use study period	1 Log increase of microbial counts in the preparation during the in-use period above T=0 baseline count may be indicative of loss of microbial quality

a Review of physico-chemical factors that can create a microbially hostile environment to help reduce microbial risk of product preparations is described in *Cosmetics-Microbiology-Guidelines for the risk assessment and identification of microbiologically low-risk products*. ISO 29621:2017.

b Review of low water activity to help reduce microbial risk of product preparations is described in USP Chapter <1112>.

Appendix II: In-use stability protocol example 1 (solid)

TABLE 3 contains the study design for the evaluation of two batches, one fresh and one aged, in support of a three-month in-use period for a product in a multi-use market package when the product has a 24-month expiry period. The three-month in-use studies on both fresh and aged samples have an intermediate time point at one month.

TABLE 3: In-Use Study Design for 3-Month In-Use Period and 24-Month Expiry

		Fresh Sample – BATCH 1			Aged Sample – BATCH 2		
Study Batches	**Actual Sample Age**	**0 Months**	**1 Month**	**3 Months**	**21 Months**	**22 Months**	**24 Months**
BATCH 1 Fresh Sample In-Use Study	**BATCH 1 In-Use Study Intervals**	0 Month* Fresh	1 Month Fresh	3 Months Fresh			
	25°C/60%RH Testing	X	X	X			
BATCH 2 Aged Sample In-Use Study	**BATCH 2 In-Use Study Intervals**				0 Month* Aged	1 Month Aged	3 Months Aged
	25°C/60%RH Testing				X	X	X

X =relevant chemical, physical and/or micro testing as selected from design section II.

* Initial testing interval for in-use study: Study packages will be opened and product dispensed.

TABLE 4 contains an illustration of the actions performed at scheduled intervals of an in-use stability study on fresh samples. TABLE 5 illustrates the same actions for the in-use stability study on the corresponding aged samples. The example requires 1 bottle for the relevant testing. Two bottles are included as reserves.

TABLE 4: In-Use Study Simulations and Time Points: Fresh Sample Study

Action	0-Month Time Point	1-Month Time Point	3-Month Time Point
STEP 1: Chamber Pulls and Testing Submission	2 unopened bottles	All 5 bottles are pulled from chamber. 1 bottle is sent for testing	Remaining bottles are pulled from chamber. 2 bottles are sent for testing
STEP 2: Sample manipulations	5 bottles are opened and product dispensed; the closed, unsealed bottles are placed in chamber	Remaining 4 bottles are opened, product dispensed, and the closed, unsealed bottles are returned to the chamber	No manipulations scheduled. Unused reserve samples (e.g. 2 bottles) are discarded

TABLE 5: In-Use Study Simulations and Time Points: Aged Sample Study

Action	0-Month Time Point (21-month age)	1-Month Time Point (22-month age)	3-Month Time Point (24-month age)
STEP 1: Chamber Pulls and Testing Submission	6 unopened bottles are pulled from chamber. 1 bottle is sent for testing.	All 5 bottles are pulled from chamber. 1 bottle is sent for testing	Remaining bottles are pulled from chamber. 2 bottles are sent for testing.

STEP 2: Sample manipulations	**5 bottles are opened and product dispensed; the closed, unsealed bottles are placed in chamber.**	**Remaining 4 bottles are opened, product dispensed, and the closed, unsealed bottles are returned to the chamber.**	**No manipulations scheduled. Unused reserve samples (e.g. 2 bottles) are discarded.**

TABLE 6 provides a comparison of sample manipulations to simulate consumer dose dispensing. The product label directs the consumer to take 2 tablets up to 3 times daily, not to exceed 10 days.

TABLE 6: In-Use Sample Manipulation Approaches

True Simulation	**Bottles are opened (seal broken) at the beginning (initial or 0-month time point) of the in-use study.** **For a total of ten (10) days, the closed but unsealed bottles are taken from the chamber.** **Two (2) tablets are dispensed from each bottle in the morning, midday, and afternoon for each of the 10 days. The dispensed tablets are discarded.** **The closed but unsealed bottles are returned to the chamber after each manipulation.**
Alternate Sample Manipulation	**Bottles are opened (seal broken) at the beginning (initial or 0-month time point) of the in-use study.** **A total of 60 tablets are dispensed from each bottle. The dispensed tablets are discarded. The bottle is left open for 15 minutes after the tablets are dispensed, after which the bottles are closed and returned to the chamber.** **The 60 tablets correspond to 2 tablets dispensed 3x daily for 10 days.** **The 15 minutes (900 seconds) exposure time corresponds to approximately 30 seconds of dispensing time 3x daily for 10 days.**

Appendix II: In-use stability protocol example 2 (liquid)

Product is packaged in a 250-mL bottle with a 24-month expiry (aspirational 36 month). In-use stability testing will be performed on samples stored at 25C/60% RH to cover the requirements for climatic zones I and II. Product label indicates treatment is considered as needed basis so both a short-term and long-term in use study are represented. The bottles will be stored in a vertical orientation (bottle with cap up).

Short-term in-use for 1 month and at expiration:

On days 1, 2, 3, 4, 5, 6 and 7, aliquots of product will be removed from previously unopened bottles stored at 25C/60% RH. After each removal, the bottles will be replaced in the 25C/60% RH chamber. At the 23- and 35-month time point, previously unopened bottles will undergo the sample removal over 7 days. After each removal, the bottles will be replaced in the 25C/60% RH chamber. The short-term design alone would typically support an in-use period of 1 Month.

1 Month Short Term In-Use								
Temp °C	**RH%**	**0 Month**	*****	**1 month**	**23***	**24**	**35***	**36**
25	60	X	Day ,1, 2, 3,4, 5, 6, 7	X		X		X
X = relevant chemical, physical and/or micro testing as selected from design section II. 0Month = incubation *Remove 10mL from all of the bottles placed on stability on days 1, 2, 3, 4, 5, 6 and 7.								

Long term in-use:

At initial and every 7 months product will be removed from all of the bottles of the sets placed on stability in the 25C/60% RH chamber, sample is discarded as per site procedure. A subset of open bottles will be tested at initial, 24- and 36-month timepoints. After each removal, the bottles will be replaced in the 25C/60% RH chamber. The long-term design could support an in-use of 24 or 36 months, dependent upon the results of the study.

Additional bottles will be kept at 25C/60% RH to be used as controls if needed. No product will be removed from these bottles.

24/36 Month Long-Term In-Use										
Temp °C	**RH%**	**0 M***	**7 M***	**12 M**	**14 M***	**21 M***	**24 M**	**28 M***	**35 M***	**36 M**
25	60	X		X			X			X
X =relevant chemical, physical and/or micro testing as selected from design section II. *Remove 10mL from all of the bottles placed on stability.										

Appendix II: In-use study design example 3

Product contains tablets packaged in a 120-mL bottle with a 24-month expiry with a 1-gram desiccant. The study design considers the requirements for climatic zones I-IVb. Marketing intelligence indicates that the product is routinely consumed within 6 months. Both a short-term (6 month) and long-term (24 month) in-use period are attempted in the study design. The bottles will be stored in a vertical orientation (bottle with cap up). This design could support a 6 month in-use, or a 24 month in-use, depending upon the results of the study.

6 Month/24 Month In-Use Design for Global Product					
Temp °C	**RH%**	**T0*§**	**6 M**	**18 M***	**24M**
25	60	X	X *6 months open BOL*	X	X *6 months open EOL and 24 months open through life*
30	75		X *6 months open BOL*	X	X *6 months open EOL and 24 months open through life*
X = relevant chemical, physical and/or micro testing as selected from design section II BOL = Beginning of Life EOL = End of Life * Remove 50% of product from defined number of containers. Invert and reset bottle 1 time and open cap for 1 minute every 7 days. Test 6 months after opening. § remove 50% of product from defined number of containers. Invert and reset bottle 1 time and open cap for 1 minute every 30 days. Test 24 months after opening.					