Central Administration of Pharmaceutical Products
General Administration For Stability

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In-Use stability testing FAQ

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Q1: What is an in-use stability study and its purpose?

In-use stability studies assess a product's quality (chemical, physical, microbiological) after it has been opened, diluted, or reconstituted to establish a period during which a multidose product can be used within an accepted specification.

Q2: Why do multidose medicinal products require in-use stability testing?

For medicines packaged in a multi-dose container applicant should provide evidence that repeated access (i.e.: opening and closing) does not affect the physical, chemical or microbiological quality of the medicine.

As repeated opening and closing, may pose a risk to its content with regard to microbiological contamination, proliferation and/ or physicochemical degradation once the closure system has been breached.

Q3: How is in-use stability data utilized in determining in-use shelf life, and what should the registration dossier for a multidose product include regarding in-use shelf-life, especially for solid oral dosage forms versus other non-sterile dosage forms?

The registration dossier for a multidose product must either include in-use stability data that supports the declared in-use shelf life or provide a scientific justification for why no such shelf life is necessary. This justification may be based on experimental data or relevant product characteristics.

For solid oral dosage forms, such as tablets or capsules, it is generally sufficient to provide a justification for the absence of an in-use shelf life. These forms are often more stable after opening due to their solid nature, which limits exposure to environmental factors such as moisture or microbial contamination. As a result, experimental in-use stability studies may not be required unless specific concerns arise.

For Example: For refrigerated bottles containing solid dosage units (e.g. capsules) specific attention should be paid to the potential moisture condensation and its impact on the medicine, sufficient data and justification should be provided to ensure the capsules integrity.

In general, a 30-day in-use period is normally considered acceptable without supporting data.

In contrast, for other non-sterile dosage forms, such as liquids, creams, or suspensions, the potential for microbial contamination or degradation after opening is higher. Therefore, in these cases, in-use stability data, often derived from experimental results, may be necessary to establish an appropriate in-use shelf life and any additional storage conditions that may be required.

Q4: What types of in-use stability studies are required for various products?

- After-opening studies: required for products susceptible to degradation or microbial contamination due to multiple use after opening.

-For medicines that may be diluted or reconstituted with a range of solutions, for example a parenteral medicine that is diluted for intravenous infusion:

a. Reconstituted products: Testing after reconstitution is essential for both human and veterinary applications.

b. After-Dilution Stability Studies: Necessary when a product is diluted before use. The study evaluates whether dilution impacts stability, and this is critical for injectables and infusions.

Q5: How long should an in-use stability study last?

The length of the in-use stability studies will depend on the intended use of the drug product. An in-use shelf life should only be set, if necessary, i.e. when significant changes as defined in ICH Q1A (R2), or veterinary VICH GL3 as relevant, are observed.

- If only one multi-dose container is needed for the treatment, the in-use studies should cover at least the length of the treatment. The study should cover the worst-case scenario in respect of the container closure system size. If more than one container is needed, one of the two bullet points below should be used for guidance.

- If the treatment is of definite length and the content of one multi-dose container will not suffice, or if the treatment is continuous without a defined end, the studies should cover at least

the time necessary to consume the content of two containers to accommodate a situation where the patient takes doses from two containers in parallel.

- If the treatment is intermittent with the dosing instruction “when needed”, the in-use studies should be designed with the aim of finding the time-point where the in-use stability fails. The study could be designed with less than daily opening of the container.

- If no relevant change is observed in the in-use study after 6 months for a product in its immediate packaging, the study does not need to be continued, and no in-use shelf life should be set. A relevant change in this context is an observed change to a quality attribute that is trending toward an out-of-specification result.

Q6: How should an in-use stability test be designed, and what factors should be considered during the testing and evaluation process?

Tests should be designed to simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/reconstitution before use. Sample withdrawal intervals should be comparable to those which occur in practice and appropriate quantities should be removed by the normal methods used and described in the product literature. This should take place under normal environmental conditions of use. Then appropriate physical, chemical, and microbial properties of the product susceptible to change during storage should be determined throughout the proposed in-use shelf life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life on the final remaining amount of the product in the container. Test storage conditions where the product should be stored under the conditions as recommended in the product literature throughout the in-use stability test period. Any other storage conditions should be justified.

Q7: What types of test parameters are required in an in-use stability study?

The appropriate physical, chemical and microbial properties of the product susceptible to change during use should be monitored. The tests used must be appropriate to the individual dosage forms, however, examples of parameter types which may need to be studied are given below:

Physical: colour, clarity, closure integrity, particulate matter, particle size

Chemical: active substance assay(s), antimicrobial preservative and antioxidant content(s), degradation product level(s), pH

Microbial: Total viable count, sterility

Q8: How many batches should be included in an in-use stability study?

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches used in the in-use stability test should be approaching the end of its shelf-life. The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing.

Q9: What if the two batches' results for the in-use stability are not available?

If results of the second batch at the end of shelf life are not available at the time of submission, before the end of the study, commitment should be provided to submit one batch study results at the final point, or after the end of the study. One batch should be tested at the final point of the submitted stability studies.

Q10: What if the product is to be supplied in more than one container size or in different strengths?

The in-use stability test should be applied in all strengths or container sizes or applied to the product which presents the greatest susceptibility to change (worst case scenario). The choice of the tested product should always be justified.

Q11: Is it required to repeat the in-use for registered products?

In general, this testing is not required to be repeated on commitment batches unless in case of shelf-life extension, a change in composition and a change in storage conditions where the conditions of shelf life and the in use were the same.

Q12 What are the key requirements for conducting and reporting in-use stability studies, including the validation of analytical procedures, data presentation, and specific considerations for registration applications?

In-use stability studies require the use of fully validated analytical procedures, particularly stability-indicating assays. The results of these studies should be summarized, tabulated, and, if relevant, presented graphically. For registration applications, quantitative results are essential, and any deviations or changes in analytical methods should be explained. Additionally, the mass balance for assay and degradation products should be considered.

Q13: What are the key considerations for validating product quality assays, including specific validation parameters, during an in-use stability study for diluted drugs, and why is it important to focus on assay sensitivity?

When validating product quality assays for an in-use stability study involving diluted drugs, the following validation parameters and considerations are essential:

1. Assay Sensitivity:

A more sensitive assay may be needed than the one used for release and stability testing. This is important because diluted drugs often require detection at lower concentrations, and a less sensitive assay might not accurately confirm potency and stability.

2. Qualification of the Assay:

The assay should be validated for the following parameters:

- Accuracy: The closeness of the test results to the true value.

- Precision: Reproducibility of results under similar conditions.

-Limits of Quantitation (LOQ): The lowest concentration of the drug that can be quantitatively detected with acceptable precision and accuracy.

- Specificity: Ability of the assay to measure the analyte in the presence of other components like excipients or degradation products.

3. Reliability at Lower Concentrations:

Special attention should be given to the assay's reliability in the concentration range expected for diluted drugs used in compatibility studies. Since the starting dose may be lowered, the assay must reliably detect and quantify the drug at these lower levels.

Focusing on these validation parameters, especially sensitivity, is critical because it ensures that the assay can accurately measure drug concentration during in-use stability studies. This is necessary for confirming the drug's efficacy and stability when diluted, preventing dosing errors or incorrect conclusions about the drug's stability profile.

Q14: What is the difference between the in-use stability & the compatibility section for pharmaceutical products?

In-use stability and compatibility are two distinct but critical aspects of pharmaceutical product evaluation, ensuring quality and safety throughout a product's life cycle.

In-use stability refers to the period during which a product maintains its safety, efficacy, and quality after being opened, reconstituted, or prepared for use. It focuses on how long the product remains stable and uncontaminated after exposure to external factors. So, the in-use stability addresses the product's behaviour after opening, in-use stability studies should be done on Pilot/ Production batches (2batches). In-use stability results should be submitted in the section (P.8).

Compatibility is a study done in development, no special requirement for batches used in the compatibility studies. It could be done on R&D samples or aged samples. It ensures the product stability and safety when interacting with external materials or during administration (Drug-Drug and/or Drug Food). Compatibility results should be submitted in the CTD section (3.2.P.2.6 Compatibility).

Both studies are essential for maintaining product integrity throughout its intended use

Q15: What if the refrigerated conditions are not suitable for the reconstituted and/or diluted medicine?

Where storage at 2-8^{0}C is not possible because of adverse effects on the medicine:

specify and justify the maximum time for storage at room temperature (not more than 6 hours).

If the reconstituted and/or diluted medicine may be kept for longer than 24 hours at 2-8^{0}C (or 6 hours at >8^{0}C):

provide data to show that when the medicine is presented with a microbial challenge (like a preservative efficacy test), ideally there is evidence of microbial death. However, the minimum requirement is demonstrating stasis (i.e. not more than 0.5 log10 units higher than the initial value of the inoculum) over the proposed storage period.

Q16: From the microbiological point of view, what is the maximum period of storage of parenteral sterile products for human after opening or following reconstitution?

For multiple-dose sterile products, a period of 28 days in-use period unless otherwise specified. This is based on successful antimicrobial effectiveness testing (AET) according to Pharmacopeial requirements. The applicant should justify the storage period and storage conditions for products after opening presented as case by case and it should not normally be greater than 28 days.

Q17: What is the data required for a period after opening in case of functional over-wrapping package in medicines?

The data required for a period after opening typically includes:

1-**Stability data:** This involves testing the product under various conditions to ensure it remains stable and effective after opening this includes chemical, physical, and microbiological stability.

2-**Storage conditions:** information on the recommended storage conditions after opening such as temperature, humidity, and light.

3-**Shelf life**: the maximum period the product can be used after opening without compromising its quality

FDA Frequently Asked Questions

Q1: How should the duration of a split tablet stability study be determined?

The duration of a split tablet stability study should be based on the anticipated routine storage conditions by the end-user. It should reflect the worst-case scenario, considering the labeling for tablet dosing and the number of tablets stored in the marketed container. The justification for this duration should be based on practices and may vary, potentially being less or more than 90 days.

Q2: What factors influence the conditions of the split tablet stability study?

The conditions of the split tablet stability study depend on several factors, including the sensitivity of the drug product to light, moisture, and oxidation, as well as how long the split portion of the tablet is stored before use. Additionally, the type of container closure system should be considered; for example, if scored tablets are stored in a blister pack, different stability conditions may be required due to the lack of a container closure for the split portion.

Q3: When is a split tablet stability study not necessary?

A split tablet stability study may not be necessary if the drug product label indicates that half tablets should be discarded (e.g., "throw away half tablets") or specifies that the second half should be dispensed the next day. In such cases, all portions of the tablet can be used for stability studies, as the split portion would not be stored for an extended period.

EMA Frequently Asked Questions

Q1: Can an open dish stability study be used to assess in-use stability?

Yes. Storage without the protection of the immediate container is considered as a worst-case scenario and can in some instances be used to assess the need for an in-use shelf life. Such studies are relevant as, in clinical practice, oral solid dosage forms may need to be stored in multi-compartment compliance aids or multi-dose dispensing packages to ensure adequate drug adherence, avoid medication errors and/or ease medication management. If no relevant change is observed after 3 months of open dish storage, no in-use shelf life is necessary. If there are relevant changes, normal in-use studies with repeated opening and closing of the container as outlined above are required to establish an in-use shelf life. The conditions of the open dish studies should be controlled for the results to be comparable. Open-dish studies at 25 °C/60% RH are acceptable without further justification as constant exposure to humidity can be regarded as a worst-case scenario.

Q2: Can an applicant apply for an in-use shelf life even if not warranted by stability results?

No, this decision is not at the applicant's discretion. Such limitations should be introduced only when strictly necessary, due to the possible implications of in-use shelf lives for patients.

Q3: What are the responsibilities of the user regarding in-use storage times and conditions for sterile products, and what are the best practices for handling these products after opening, reconstitution, or dilution?

It is always important to highlight that in-use storage times and conditions are the responsibility of the user and it is also preferred that sterile products for human use after first opening or following reconstitution or dilution are to be used immediately. However, the MAH should establish in-use shelf-life periods based on the needs in actual practice for the cases the method of opening/reconstitution/dilution precludes the risk of microbial contamination and the prepared ready to administer product can be stored for longer periods.

It should also be noted that storage in a refrigerator after first opening/reconstitution/dilution is best practice unless it has been demonstrated that the product cannot be refrigerated (the warning is accordingly added in the Product Information).

Q4: When should the "Specific text for preparations for infusion or injection" be used?

The "Specific text for preparations for infusion or injection" should be used for unpreserved sterile products for infusion or injection where:

- The chemical and physical in-use stability has been demonstrated for >24 hours and

  Stability at 2 to 8°c has been demonstrated.

Example

Data provided in the dossier demonstrated chemical and physical in-use stability for 36 hours at +2°C to +8°C and for 18 hours at +25 °C.

Recommended wording:

"Chemical and physical in-use stability has been demonstrated for 36 hours at 2 to 8°C or for 18 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution (etc.) has taken place in controlled and validated aseptic conditions."

NB: It should be kept in mind that the prepared ready to administer product can be stored for up to 36 hours at +2°C to +8°C or for 18 hours at +25 °C only if reconstitution / dilution (etc.) has taken place in controlled and validated aseptic conditions. In all other cases the product must be used within 24h and it must be stored only in a refrigerator.

Q5: When is the wording for Aqueous preserved (including intrinsically self-preserving) sterile products and non-aqueous?

This wording applies for multidose sterile products which contain preservative and for sterile products which are intrinsically self-preserving e.g. eye drops.

Preservative effectiveness (according to the Ph. Eur.) should be demonstrated during development using drug product samples where the preservative concentration is at or below its lower specification limit and when intrinsic self-preserving properties are claimed.

The in-use stability declared in the Product Information should be based on the results of chemical, physical, and microbiological in-use stability tests demonstrated in the MA dossier. This should always include evidence or scientific rationale to justify whether the product can or cannot be stored at 2 to 8ºC.

The in-use shelf life should be clearly stated and be based on either physical and chemical stability or microbiological stability, whichever is shorter.

Example

Data provided in the dossier demonstrated microbiological stability for 28 days and chemical and physical stability of 3 days.

The acceptable in-use shelf-life is 3 days. 28 days should not be mentioned in the Product Information.

If the reconstituted/diluted product cannot be refrigerated the statement “Do not refrigerate” should be added.

The recommended wording:

“Chemical and physical in-use stability has been demonstrated for 3 days at 25°C. Once opened, the product may be stored for a maximum of 3 days at 25°C. Other in-use storage times and conditions are the responsibility of the user. Do not refrigerate (if applicable).”

Q6: Is it allowed that the in-use stability of one product deviates from other authorized products (e.g. regarding storage time, storage conditions)?

In principle, each product will be assessed on its own merits and differences may exist. However, when the difference in in-use stability and/or compatibility potentially leads to detrimental medication errors in daily practice, such a difference cannot be accepted.

References

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5- Australian regulatory guideline for over-the-counter medicines Appendix 2: Guidelines on quality aspects of OTC applications https://www.tga.gov.au/sites/default/files/argom-appendix-guidelines-quality-aspects-otc-applications.pdf-٢

6- Stability by Daan Touw, Judith Thiesen, Jean Vigneron. 2023, Practical Pharmaceutics, p. 809-837;https://research.rug.nl/en/publications/stability-2