

Guidelines on Stability of Pharmaceutical Products, 2007

DDA has been implementing the WHO guidelines on stability testing in phased manner. Cooperation of the industry and progress made in implementing the stability requirement is praiseworthy. All manufacturers are requested to adopt the WHO working document QAS/06.179/Rev.1 on "Stability testing of active pharmaceutical ingredients and pharmaceutical products, 2007" as far as possible. **However the following is the minimum requirement that has to be complied for applying for marketing authorization of the product on or after Shrawan 1, 2064.**

1. Accelerated stability testing on two batches should be conducted, one of which must be either commercial batch or a pilot-scale batch. A pilot batch should not be smaller than one eighth of the commercial batch. If accelerated stability testing was carried out on one laboratory batch, which was produced by similar manufacturing process and has the same composition of active ingredient/s and excipient/s as for the commercial batch, accelerated stability test on single commercial or pilot-scale batch should be acceptable. Accelerated stability testing should be done on 0, 3 and 6 months.
2. Initially real time stability testing should be conducted on two batches for the expected shelf-life of the product, one of which should be commercial batch. One batch can be a pilot scale batch. Continuing real time stability study should be carried out on subsequent batches, as per the schedule and standard operating procedure approved by quality assurance department of the industry, taking into consideration any changes like equipment, process and source of raw material etc. Real time stability testing should be done on 0, 3, 6, 9 and 12 months on first year, every six-month on second year and once every year afterwards.
3. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label).
4. Stability studies should include testing of those attributes of the pharmaceutical product that are susceptible to change during storage and are likely to influence quality, safety, and efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative). Analytical procedures should be fully validated and stability indicating.
5. One initial batch of the pharmaceutical product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf-life for verification purposes.
6. If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf-life should be based on the real-time data available from the long- term storage condition.

In general, "significant change" for a pharmaceutical product is defined as:

- a. **A 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures.**
- b. **Any degradation product exceeding its acceptance criterion.**
- c. **Failure to meet the acceptance criteria for appearance and physical attributes (e.g. colour, phase separation, re-suspendibility, caking, hardness). However, some changes in physical**

attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

- d. Failure to meet the acceptance criterion for pH (for liquid preparation).**
 - e. Failure to meet the acceptance criteria for dissolution for 12 dosage units (tablet and capsule).**
7. Stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.
8. If no significant change occurs during six-month's accelerated and real time stability testing, the product will be allowed to place in the market with a provisional shelf-life of up to twenty-four months. However, real time stability testing should be continued up to the proposed shelf-life. The manufacturer should have a system of recall in place so that the sale any batch which does not remain within the limit of approved product specification be stopped within twenty-four hours.

Expiry date

The date given on the individual container (usually on the label) of a product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

9. Once the pharmaceutical product has been registered, additional stability studies are required whenever variations that may affect the stability of the active pharmaceutical substance or pharmaceutical product are made, such as major variations like the following:
- a. Change in the manufacturing process.
 - b. Change in the composition of the pharmaceutical product.
 - c. Change of the immediate packaging.
10. The ongoing stability programme should be described in a written protocol, and results formalized as a report.
11. Condition of Climatic zone IV A will be applicable for Nepal, though the WHO document mentions Climatic Zone II. Condition for real time stability testing: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$; condition for accelerated stability testing: $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$.

Parameters for stability testing

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. In general, - appearance, - assay and - degradation products should be evaluated for all dosage forms, as well as preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular pharmaceutical product (for example, a test for odour should be performed only when necessary and with consideration for the analyst's safety).

1. Tablets

Dissolution (or disintegration, if justified), water content and hardness/friability. For coated and coloured tablets additional tests may require for texture and colour stability.

2. Capsules

Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content, and level of microbial contamination.

3. Emulsions

Phase separation, pH, viscosity, level of microbial contamination, and mean size and distribution of dispersed globules.

4. Oral solutions and suspensions

Formation of precipitate, clarity for solutions, pH, viscosity, extractables, level of microbial contamination.

Additionally for suspensions, redispersibility, rheological properties, mean size and distribution of particles should be considered. Also, polymorphic conversion may be examined, if applicable.

5. Powders and granules for oral solution or suspension

Water content, and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described in "Oral solutions and suspensions" above, after preparation according to the recommended labelling, through the maximum intended use period.

6. Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractable/leachable from plastic and elastomeric components of the container, closure and pump.

7. Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops, and cutaneous sprays.

Topical preparations should be evaluated for clarity, homogeneity, pH, resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable.

Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content, and particle size distribution (for suspensions).

8. Suppositories

Softening range, dissolution (at 37°C).

9. Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labelling, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter.

The stability studies for Suspension for injection should include, in addition, particle size distribution, redispersibility and rheological properties.

The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

10. Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin, and volume.

Minimum requirement for applying for the marketing approval of the product

1. Accelerated stability test result for at least one commercial batch, or pilot-scale batch intended to be placed in the market and produced using the same equipment and process approved for commercial batch. Accelerated stability testing should be done on 0, 3 and 6 months.
2. Real time stability study reports for 0, 3 and 6 month for the same batch for which accelerated stability testing is carried out.
3. Real time and accelerated stability test report should be self-explanatory and conclusion should be mentioned on the report.
4. Report of analysis from National Medicines Laboratory for the same batch for which accelerated stability report is being submitted.

Guidelines issued on Friday, Asadh 1, 2064 (June 15, 2007)