

Standard Operating Procedure

Title: Preparation and Maintenance of Stability Protocols

specify exactly what the limits are. The Release Limits shall specify 'As lifetime', if they are identical to the Registered Lifetime Limits. If the Release Limits differ from the Registered Lifetime Limits, then the Release Limits shall be specified exactly.

- 2.4.2. For tests that have different Registered Release Limits and Registered Lifetime Limits for different markets, those limits shall be listed by country. The release and stability limits, and methodology used for stability testing shall be obtained from the regulatory approved documentation. These regulatory approved documents for the release and stability Limits shall be listed on the initial version of the Integrated Stability Protocol. If any of these documents are updated with major changes such as specification or method changes, the integrated protocol should be amended to reflect the new version numbers. However, it is not necessary to create a new version of the integrated protocol if the modules are updated as a result of minor changes.
- 2.4.3. The stability site reference numbers applicable to methods and limits may be listed. This listing is optional.
- 2.4.4. If any Release Limits and/or Registered Lifetime Limits change for a product, its Integrated Stability Protocol shall be revised and approved.
- 2.4.5. If any tests are added or removed or if the Set Down Limits and/or OOS Reporting Limits change for a product, its Integrated Stability Protocol shall be revised and approved.

2.5. Integrated Specifications

- 2.5.1. An Integrated Specification shall contain all tests required for product release and stability studies, together with their associated Set Down Limits and OOS Reporting. The tests and their associated limits shall be presented in tabular form.
- 2.5.2. The Set Down Limits shall be the manufacturing limits submitted at the time of registration. Where manufacturing limits were not registered, the Set Down Limits shall be the Registered Lifetime Limits. The Set Down Limits shall specify 'As lifetime', if they are identical to the OOS Reporting Limits. If the Set Down Limits differ from the OOS Reporting Limits, then the Set Down Limits shall be specified exactly. Where several market specific limits exist and are applicable to the particular Pack Code combinations that the Integrated Specification refers to, the Set Down Limit shall be the tightest manufacturing limit for each test parameter in order that studies will satisfy all regulatory submissions.
- 2.5.3. The OOS Reporting Limits are the Registered Lifetime Limits as registered in regulatory submissions. In cases where there are several market specific specifications applicable to the particular product/pack combinations, the OOS Reporting Limits shall be the tightest lifetime limit for each test parameter in order that studies will satisfy all regulatory submissions. These limits shall be met to satisfy the expiry life of each product/pack combination.
- 2.5.4. The Integrated Specification shall specify which tests are done on the initial sample only, initial and final test points, and at all test points.
- 2.5.5. If any tests are added or removed or if the Set Down Limits and/or OOS Reporting Limits change for a product, its Integrated Stability Protocol shall be revised and approved.
- 2.5.6. Test Parameters - a justification shall be provided for the inclusion and exclusion of particular test parameters from the protocols.
- 2.5.7. Derivation of the Integrated Specifications - an explanation for the Integrated Specifications for the set down and OOS reporting limits shall be provided.
- 2.5.8. Bulk Pack Code Containers - a simulated pack shall be utilised to reflect the drums or other containers that are actually used to store bulk Drug Substances and/or the bulk tablets for stability set downs. The simulated pack shall be smaller than the actual drums/containers but shall be of identical or equivalent composition, (e.g., liner and fibre material).