Annex

Q&A on Stability

Q :
If the stability data from commitment batches under the ASEAN long-term conditions, i.e., 30°C ± 2°C/75% RH ± 5% RH, indicate that the product might not meet the required specification at the approved shelf life, what options can an applicant consider and, if a reduced shelf life is contemplated, how can the new shelf life be calculated?

A:
The applicant can consider one of the following options, *if justified*: (1) reduce the shelf life based on long term stability study; (2) develop a more protective packaging; (3) add a more restrictive storage statement in the labeling supported by adequate data based on conducted stability study, e.g., "Store below 25°C" or "protect from moisture;" (4) revise the acceptance criteria on stability indicating parameters based on scientific justification (Note: for drug product listed in the Pharmacopoeia, the specification must follow the Pharmacopoeia).

Reduction of Shelf Life

If reduction of shelf life is desired, the following approach can be considered:

Reduction of Shelf Life using Data under ASEAN Stability Condition (30°C ± 2°C/75% RH ± 5% RH)

An example is provided below to illustrate how an applicant may reduce a product shelf life and what kind of analysis can be performed.

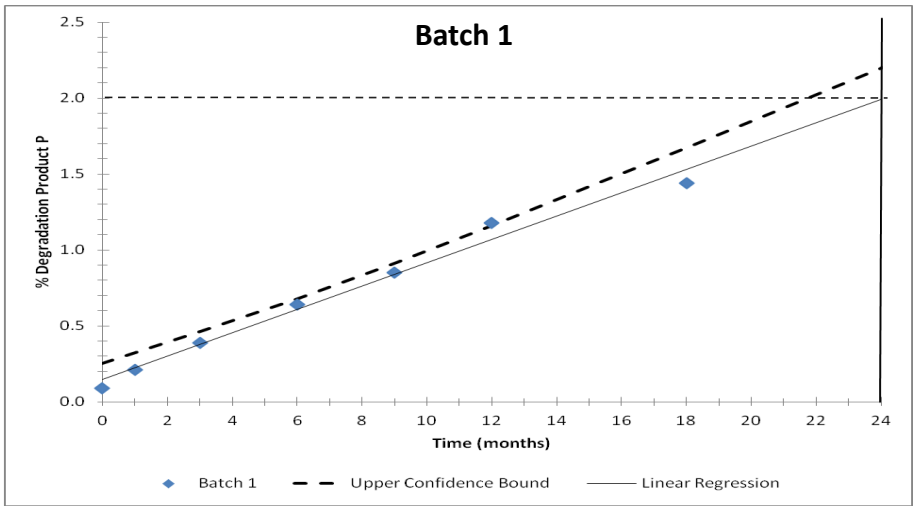
Background

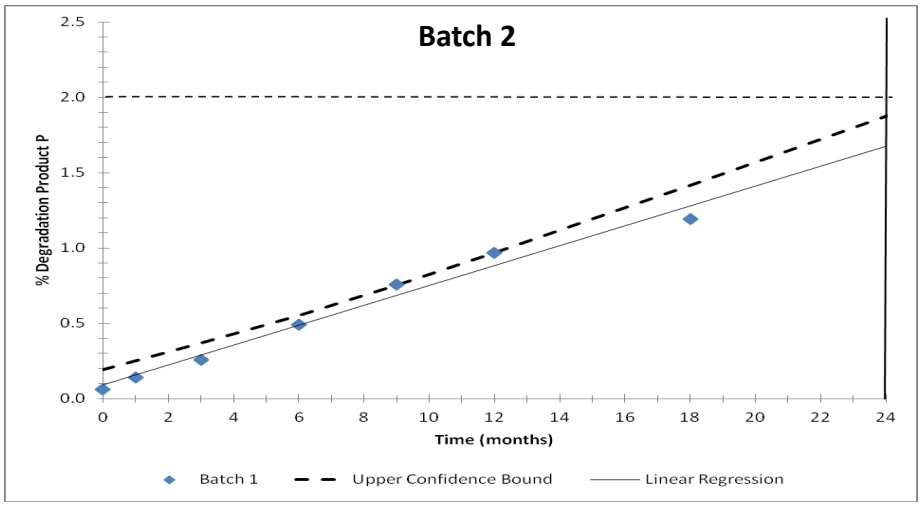
- The applicant received approval for its Product X with a 24-month shelf life and an acceptance criterion of 2.0% for Degradation Product P.
- After placing the first 3 commercial batches on long-term stability for 18 months, the level of P appeared to be increasing at a higher rate than observed in the registration batches. See Table 1.
- Statistical analysis of the 18-month data on P from the 3 batches, following ICH Q1A(R2) and Q1E (Appendix B, Sec 1), showed that the upper one-sided 95% confidence limits of the linear regression lines intersect the 2.0% acceptance criterion at 21.5, 25, 22.5 months for Batch 1, 2, and 3, respectively. See Figure 1.
- A test for poolability of the 3 batches using ANCOVA (ICH Q1E, Appendix B, Sec 2.2.1) indicated that these batches cannot be combined to estimate a single, longer shelf life.

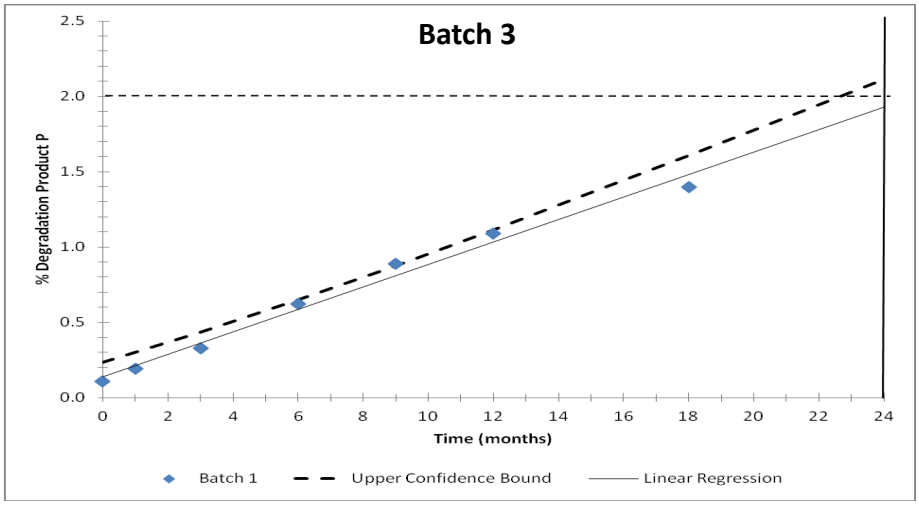
Table 1: Data of degradation product P from commitment batches at ASESAN stability condition

	Level of Degradation Product P (%)						
Time (month)	**0**	**1**	**3**	**6**	**9**	**12**	**18**
Batch 1	0.09	0.21	0.39	0.64	0.85	1.18	1.44
Batch 2	0.06	0.14	0.26	0.49	0.76	0.97	1.19
Batch 3	0.11	0.19	0.33	0.62	0.89	1.09	1.40

Figure 1: Shelf life estimation by batch using statistical analysis







Proposed shelf life

The applicant proposed to shorten the shelf life of Product X from 24 months to 18 months based on the new data on P and their statistical analysis:

- Since the batches could not be pooled for a single estimate, the shortest estimate among the batches should be chosen as the shelf life for all batches. In other words, a shelf life of 21 months can be justified based on the worst case, Batch 1.
- However, for practical reasons, the shelf life will be set to 18 months, instead of 21 months, because 18 months is a testing time point and 21 months is not (unless the stability protocol is revised to include a 21-month testing point).