Stability Guidance & Draft Q&A Guidance - considerations

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Agenda

- ANDA Stability Guidance – Recent activities
- several questions are received for the draft stability guidance
  - Common considerations
  - Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (presented at the FDA-GPhA Spring workshop in 2012, 2013)
  - Amendments to pending ANDAs
  - Exception criteria from batch size for pilot scale
  - Q1E Evaluation of stability data – considerations, recommendations
  - Summary

Webinar

Recent activities

- Finalization of the ANDA stability guidance is completed and announced on June 20, 2013; The implementation date for the ANDA stability guidance is announced as June 20, 2014 in the draft Q&A guidance
- The Stability guidance is for Original ANDA submissions and the Q&A is for providing implementation support; Draft Q&A guidance addressing several questions (sent in to Docket) has been published on August 26, 2013;
- FDA-GPhA Spring Technical workshop (June 2013) hosted two FDA speakers presenting responses to industry questions (who are also conducting today's Webinar)

Common Considerations

- Sterile drug product batches (supporting ANDA submission) should be manufactured in a sterile facility (sterility is a critical product quality attribute)

- Time points for various storage conditions:
  - 0 = initial release
  - Accelerated time points: 0, 3, 6, and one additional time point
  - Intermediate time points (0, 6, 9, and 12 months)
  - Long-term time points (0, 3, 6, 9, 12, 18, 24, 36 months)

- For Supplemental ANDA submission requirements – refer to SUPAC IR/MR/SS, and Changes to an approved NDA or ANDA guidance, and Q&A to Changes guidance

Drug Product -Bracketing

- No change from current policy – for Bracketing
- Test only the samples on the extremes of certain design factors (container size/fill/strength) at all time points as in a full design
- Bracketing - experience is great!
  - Time-tested in OGD – ANDA Products are already following this concept
  - Reasonably safe design- multiple batches (3)
  - Extremes of design factors (strength/ fill volume/count size) are tested at all times as in a full design

Considerations for Bracketing

- Change in containers/void volume change/wall thickness/geometry – characteristics should be comparable
- If one of the extremes is no longer expected to be marketed study design needs to be maintained to support intermediates
- The shelf-life of the intermediates should not exceed that of the least stable extreme
- Bracketed strength will need initial full release testing, and Bio waiver request (if eligible)

Example of a Bracketing Design

- Q1D

Table 1: Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

Matrixing Considerations

- Matrixing can be implemented with out a pre-approved protocol – when ICH guidances are implemented.
- Due to data coming from 3 batches, example tables presented in the Q1D guidance can be adopted
- Assumes stability of each subset of samples tested represents the stability of all samples at a given time point
- Recommends full testing at certain time points (e.g., 0, 12, 24, 36 months etc..)
- More suitable for long-term testing protocols than accelerated, or intermediate testing

Matrixing Considerations

- Degree of Reduction from Q1D- Matrixing guidance depends on
  - Knowledge of data variability
  - Expected stability of the product
  - Availability of supporting data (including pre-formulation studies/excipient compatibility studies/stress studies)
  - Stability differences in the product within factor or among factors
  - Number of combinations in the study

  [1/2 reduction could be too much and 3/4 testing may be just enough]

Applicability

- Factors that can be matrixed
  - Batches – common blend
  - Identical formulations
  - Container sizes
  - Fill sizes
  - Closely related formulations (see Q1D) – colorants/flavors
  - Container closure suppliers if justified
- Factors that should not be matrixed
  - Initial and final time points
  - Test parameters (attributes)
  - (Dosage forms)
  - Storage conditions
  - Strengths w/ different formulations (different excipients or different active/excipient ratios)

Q1D Guidance Example

Tables 3a and 3b: Examples of Matrixing Designs for a Product With Three Strengths and Three Container Sizes

3a Matrixing on Time Points

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

3b Matrixing on Time Points and Factors

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key:

Time-point (months)	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

S1, S2, and S3 are different strengths.
A, B, and C are different container sizes.
T = Sample tested

Additional Considerations

- ANDAs with several strengths (e.g., 3 or more than 3)
  - Matrixing designs possible as this example from previous slide (#11) can be duplicated and used
  - Matrixing examples illustrated in the Q1D guidance are all based on 3 batches (are made) for each strength
  - Multiple strengths are to be submitted at the same time in order to use Matrixing designs
  - Multiple strengths divided among original submission and unsolicited (major) amendments may not qualify/be suitable for matrixing protocol
  - Alternatively a suitable Bracketing design can be proposed – to be discussed in the next slide

Q1D Consideration

- Case where common granulation/blend is used (tablet/capsule), is there a need to make three batches of each strength? (Section C Q&A 19)
- The following is our current thinking:
  - Three separate common granulation/blends to be made
  - one batch per ICH (at least of pilot scale) needs to be manufactured comprising of all strengths (using one of the three common blend batches); the other two batches of common granulation/blend can be used for the highest and lowest strength alone; in the event BE studies are done on a different strength (i.e., a strength that is neither highest or lowest), that needs to be included also in the manufacturing from all three common blend
  - Then a Bracketing design can be used to stability test strengths and all (3) batches, where smallest and largest container fill size alone can be subjected
  - At the time of original ANDA submission present all strengths

Example of multiple strengths protocol (q&a 19) from the draft guidance

Ropinirole HCl Tablets: Common granulation/blend approach:

Strength in mg	2	4	8	10	12
Batch #1	x	x	x	x	x
Batch #2	x	None	None	None	x
Batch #3	x	None	None	None	x

x: strength manufactured; Batch 1, and 2 should be at least of Pilot size (per ICH definition), i.e., 10% of proposed commercial scale or 100,000 units whichever is larger.
Batch 3 can be smaller; for small batch size definition see draft Q&A guidance.

x: The color-coded strengths alone are stability tested and all the intermediate strengths are bracketed; stability testing to be conducted in accelerated, long-term and intermediate (if needed).

We recommend providing all release testing information (COA) on all strengths (2, 4, 8, 10, 12 mg) on Batch #1 and request a Biowaiver for the intermediate strengths. In addition, COAs for 2 mg and 12 mg strengths from Batch #2 and #3 are needed.

Amendments to pending ANDAs

- Q&A guidance section D
  - "All amendments submitted to pending ANDAs after the effective date of the final stability guidance (June 20, 2014) will be held to the standards in place at the time of the original ANDA submission, unless there is a concern with the submitted stability data."
    - An original ANDA which is filed prior to the June 20, 2014 implementation date would only require stability data for one batch per strength for submission. If additional strengths are amended to this ANDA after the June 20, 2014 implementation date, the assumption is that stability data for only a single batch per strength would be required for submission. - Yes, but will be considered a major amendment
    - If a firm were to submit an original ANDA after the June 20, 2014 implementation date, and additional strengths are to be submitted as an amendment, how many batches of stability data will be required? - # 3 batches will be required and it will be considered a major amendment; if all strengths are filed with the original anda then see slide # 14.

Exceptions to batch size from ICH definition

- Q&A # 20: What are the exception criteria from meeting the minimum size for pilot scale recommendations for ANDA submission batches? What justification would be needed if we wanted to deviate from the guidance recommendation?

  - Exemption for Orphan drug designation
  - Use of controlled drug substance
  - Test batch size is same as the commercial batch size with the commitment a prior approval supplement will be filed when there is scale-up

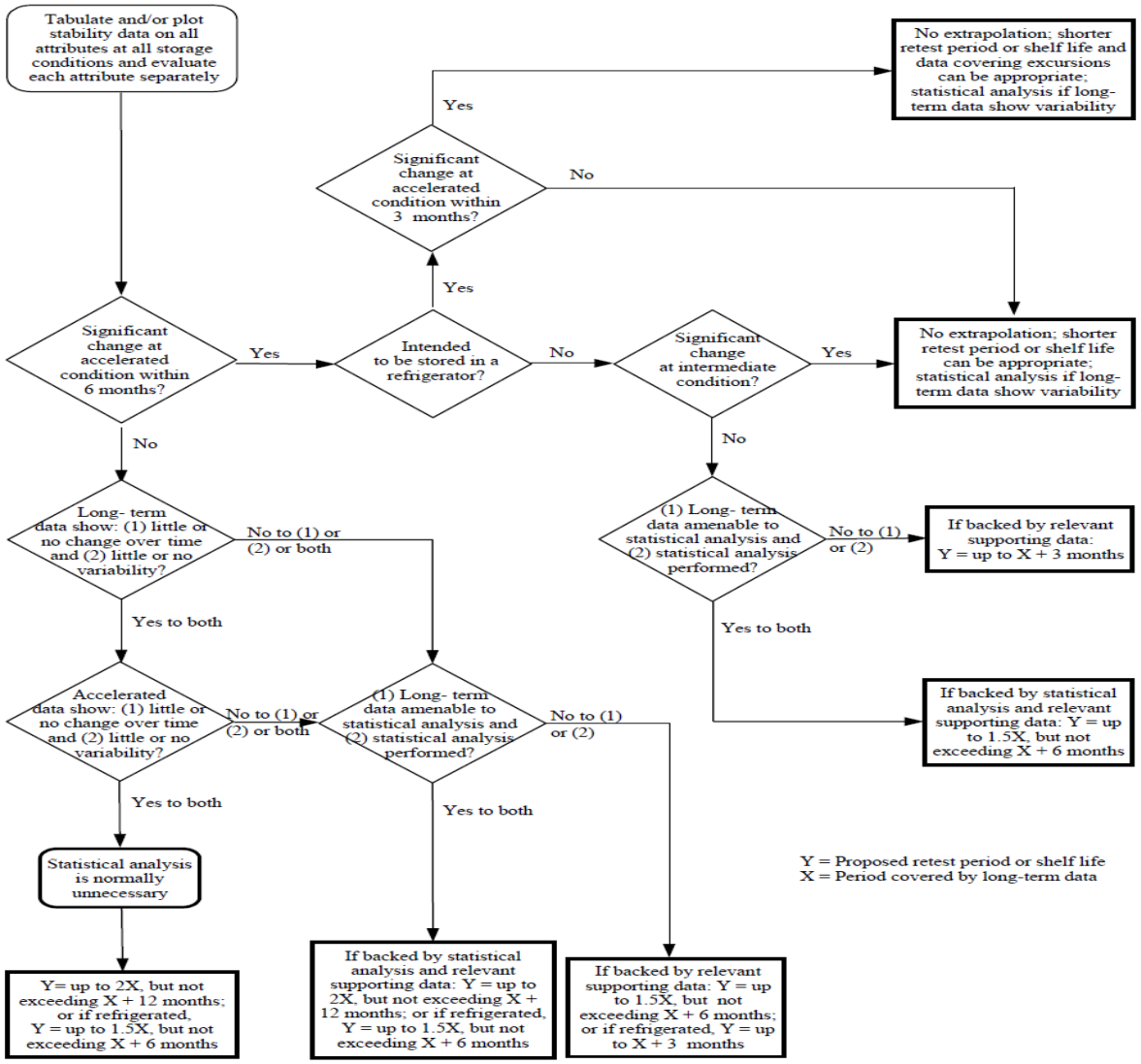
Q1E Considerations

- What are the expectations for data analysis and evaluation?
  - All three batches' data to be presented
  - Use of Appendix A: Decision Tree for retest period or shelf life estimation (excludes frozen Ds/Dp)
  - Use of tables, narrative, graphs, and analysis where needed to propose expiration dating (DP), and retest date (DS)
  - Graphical format for assay, impurities/deg. p/total impurities, and other critical attributes (e.g., pH), vs. time pts with upper and lower limits
  - Consideration of Significant Change from ICH Q1A(R2) section 2.2.7.1
  - At the time of submission 6 months accelerated data, and 6 months long-term data to be provided for all 3 ANDA submission batches
  - Submission batches should be made under CGMP, and packaged using automated/similar to commercial packaging lines, to provide adequate protection for the DP

Q1 E Consideration- continued

- If 6 months accelerated data fails/significant change occurs, ANDAs will need 6 months 30°C/65%RH intermediate data on batches at filing time for all 3 ANDA submission batches
- Narrative to be provided addressing the above
- Expectations are the same as those outlined in Q1E Guidance

•Appendix A – Decision Tree for Data Evaluation



Q1 E Considerations

- Statistical analysis need not be performed when 6 months accelerated data show no significant change and long term data show no variability. A stable drug product meeting the above will not require statistical analysis, per Appendix A.
- OGD will continue to grant 24 months tentative expiry based 6 months accelerated, and 12 months (or more if available) long-term data (if the above is met)
- Significant change occurs between 0 and 6 months, long-term data needs to be used for analysis **and** intermediate data are required (30 °C/65% RH – 6 months at the time of ANDA submission, and 12 months' to be amended)

Intermediate Data Evaluation

- 6 months at filing (0/initial, and 6)
- If intermediate data also fails (meaning significant change at that condition)

  -No extrapolation of shelf-life/retest date

  -Long-term data alone will take over shelf-life/retest determination

Q1E Continued

General approach – When stat. analysis is needed

- Boxes in the Appendix A cite stat. evaluation, and when data shows variability

- Data evaluation approaches

  Linear, logarithmic etc.; long-term data

  -If the relationship is linear between attribute and time then linear regression is a preferable mode

  -Linear regression model is popular and applicable when linear potency loss or increase in degradation observed

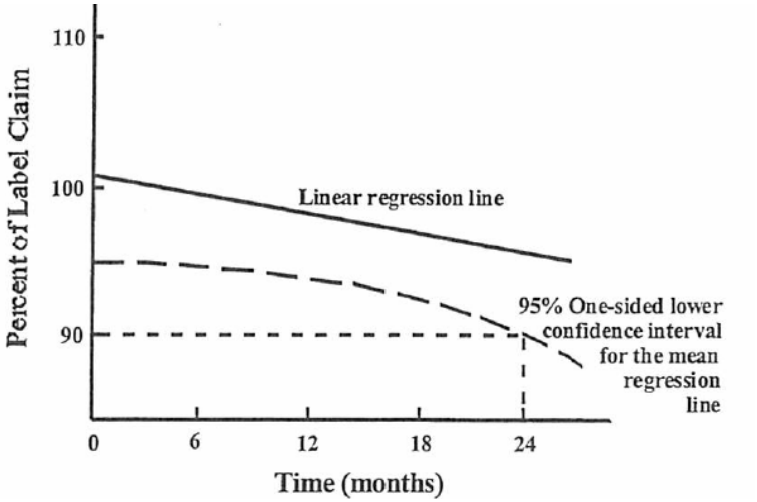
Data Analysis Expectation

- Plot the long-term data for a given attribute (e.g. assay) vs. time (in months) for 3 batches
- Determine the time when 95% confidence interval intersects the proposed acceptance criteria
- Considerations of data poolability and significance level (p)
- Individual batches are to be used and shortest expiry needs to be proposed

Graph Expectations

- One-sided 95% Confidence limit curve when time vs. acceptance criterion is plotted; at times two-sided will be needed
- Data poolable vs. non poolable
  - Small batch to batch variability = data to be pooled
  - Large variability = not recommended for pooling
  - In general common slopes and a common time-zero intercept may mean that data from batches can be pooled

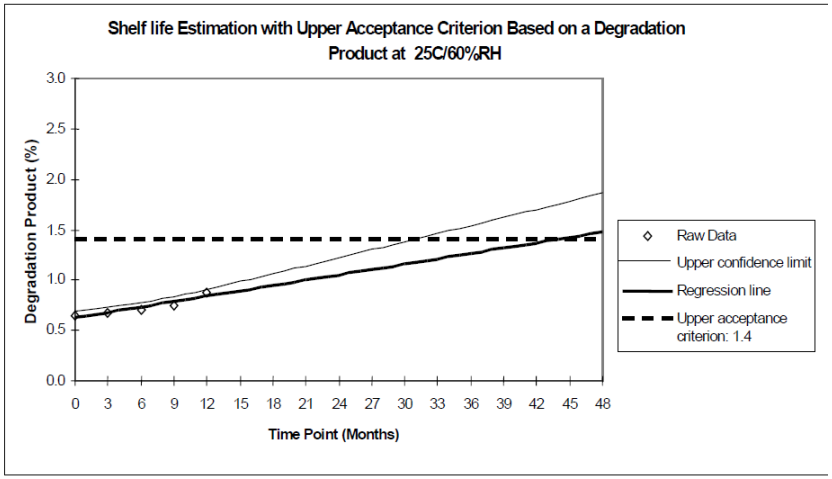
Data Presentation

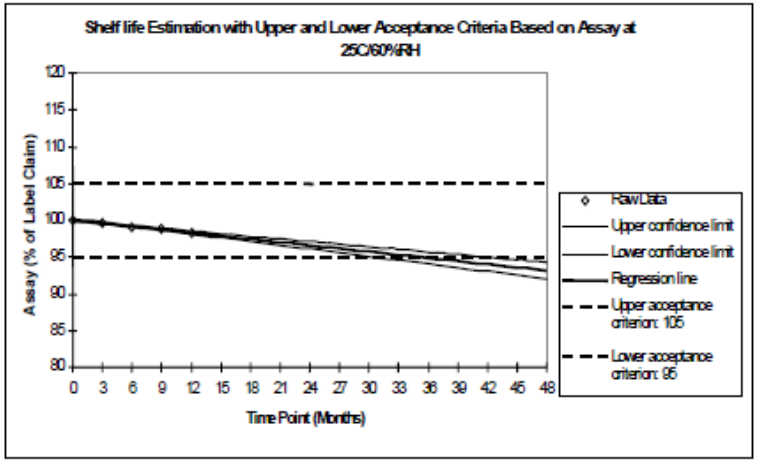


- The concept of one-way and two-way 95% confidence limits of the regressed stability lines are presented as examples
- Assay value Vs. time in months (one-sided lower CI reg. line)
- Degradation product value Vs. time in months (one-sided upper CI reg. line)
- Two-way CI line example

Data Presentation

Figure 2





Q1E Continued

- Setting Expiration (Drug product)
- Retest date (Drug substance)
  - Long-term data to be used for stat. analysis
    - Data amenable to statistical analysis (2 times LT but not more than 12 months, and if refrigerated NMT 6 months)
    - Data not-amenable to statistical analysis (1.5 times LT, but not more than 6 months and if refrigerated NMT 3 months)

Summary

- Developing a stability protocol utilizing Q1 D (Bracket or Matrix) guidance is essential to a successful program
- Batch size exceptions are noted in the Q&A guidance

- Key Q1E notes:
  - Application of significant change, generation of ICH intermediate condition data (when needed), and utilization of all 3 batches' stability data
  - Stable drug product (6 months 40°C/75%RH, and no variability at long-term) will not need data analysis
  - Narrative, and graphical presentation of data (in addition to tables, where assay, impurities can be plotted individually), needed
  - Data analysis needed as indicated by Appendix A – when products experience significant change, using long-term data tentative expiration is to be proposed

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