An Industry Perspective on Shelf Life and the PQRI Initiative

Pat Forenzo
Novartis Pharmaceuticals
PQRI Stability Shelf Life Working Group
Agenda

• Background on Purpose and Design of Stability Studies
• Shelf life estimation as per ICHQ1E
• PQRI Working Group
Basics

- For the purpose of this presentation we will be considering a solid dosage form drug product intended for storage at room temperature.
- The theory and procedures apply to all drug substances and drug products formulations intended for storage at room temperature.
- DP and DS intended for storage at 5°C and -20°C (or below) differ only slightly in the degree of extrapolation (if any) allowed.
Stability Studies

The purpose of a stability study is to test and document the effect of environmental factors such as

- temperature
- humidity
- light

on the physical and chemical properties of a drug product/drug substance and to establish a shelf-life and recommended storage conditions based on the effect of these factors on the drug product over time.
Stability Studies

Other factors studied for effect on product stability include:

• the effect of packaging type
  • Bottles vs. Blister
  • Less protective Blisters (PVC) vs. more protective blisters (Aluminum-Aluminum)
• number of units per container (headspace)

The shelf-life and label storage instructions are applicable to all future batches manufactured and packaged under similar circumstances.
Batch Information

- Primary stability studies (Registration Stability) require a minimum of 3 batches - at least 2 pilot scale and 1 can be smaller but not lab scale.
- For DP, it is recommended, that a different lot of drug substance is used to manufacture each of the 3 batches.
- Multiple strengths (if similar formulations) may be combined into 1 study.
Storage Conditions

**Long term testing**
Stability studies performed under the recommended storage condition (25°C/60%RH) to establish shelf life for the product.

**Frequency**

• Every 3 months for first year, every 6 months for second year and annually thereafter.

**Example**

0, 3, 6, 9, 12, 18, 24, 36, [48, 60] months
Storage Conditions

**Accelerated testing (40°C/75%RH)**

- “Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies” (ICHQ1A(R2))

- Results from accelerated testing studies are not always predictive of the degree or rate of chemical degradation or physical changes observed during storage at the long term storage condition.
Storage Conditions

**Frequency**

- Minimum of 3 time points, including initial and final points
  - Example typical stability study: test at 0, 3 and 6 months)
Significant change

• 5% change in assay value from its initial value or failure to meet acceptance criteria for assay
• Any degradation product exceeding its acceptance criteria.
• Failure to meet acceptance criteria for appearance, physical attributes, and functionality test.
Storage Conditions

**Intermediate testing (30°C/65% RH)**

Studies conducted at less severe conditions than the accelerated condition but more severe than the long term storage condition. Testing is triggered when a significant change is observed at accelerated condition.

**Frequency**

Tested only when a to “significant change” at accelerated conditions is observed, a minimum of 4 time points including initial and final time points. Testing starts at the timepoint where the significant change is observed during accelerated condition testing.
Storage Conditions

**Intermediate testing (30°C/65% RH)**

Example: Significant change is observed at 6 month timepoint for 40°C/75%RH

Intermediate study: test at 0, 6, 9, 12 months
ICH Storage Conditions for Formal Stability Studies

ICH General Storage Requirements (Zones 1 and 2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
<th>Minimum time period covered by data at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25°C ± 2 °C / 60%RH ± 5%RH</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30°C ± 2 °C / 65%RH ± 5%RH</td>
<td>12 months (if applicable)</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2 °C / 75%RH ± 5%RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>
How much data is available at filing for estimating a shelf life?

A typical study consists of 3 batches and may contain 3 bottle counts and 1 blister pack for a total of 4 packages,

A study of this size would yield:

Long-term storage (25°C/60%RH)

• 5 time points (0, 3, 6, 9 and 12 months)
• 3 data points at $T_0$ (one for each batch)
• 12 data points at each of the other 4 time points (one for each batch / package combination)
• 51 total data points
How much data is available at filing for estimating a shelf life?

- Accelerated condition storage (40°C/75%RH)
  - 3 time points (0, 3 and 6 months)
  - 3 data points at T₀ (one for each batch)
  - 12 data points at each of the other 2 time points (one for each batch/package combination)
  - 27 total data points
Establishing a Shelf Life

Statistical evaluation is not necessary if it is apparent from the data that drug product will stay within the acceptance criteria for the proposed shelf-life. A shelf life of up to 2 times the available long term data but not more than $x + 12$ months can be proposed.

For example if filing with 12 months data and it is clear from looking at the accelerated and long term data, that the drug product is stable and shows little to no variability, a shelf life of 24 months can be proposed without performing statistics to support the proposal.
Statistical Evaluation

An approach for analyzing data is to determine the time at which the 95 one-sided confidence interval for the mean curve intersects the acceptance criteria.

If analysis shows that the batch to batch variation is small, it is advantages to combine data into one overall estimate. This can be done by first applying appropriate statistical test to the slopes of the regression lines and zero time intercepts for the individual batches. The shelf-life obtained from pooled data is generally longer than from unpooled data.
Extrapolation

Limited extrapolation to extend the proposed shelf-life beyond the observed range of available long term data (25°C/60%RH) can be proposed if no significant change is observed at the accelerated condition (40°C/75%RH).

An even more limited extrapolation can be used if the product shows significant change at the accelerated condition (40°C/75%RH), but subsequent testing at the intermediate condition (30°C/65%RH) remain within specification.
ICH Decision tree

ICH Q1E contains a decision tree in the form of a flow chart that provides guidance on setting shelf life based upon the results for accelerated, intermediate and long term storage conditions.

The flow chart establishes a proposed shelf life, statistical analysis is then used to confirm that the available data supports the proposed shelf life.

Statistical analysis can only confirm or shorten the proposed shelf life, it cannot be used to extrapolate beyond what the decision tree allows.
ICH Q1E Appendix A
Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products

Significant change at accelerated condition within 6 months?

Yes

Significant change at intermediate condition?

Yes

No extrapolation: shorter retest period or shelf life can be called for; statistical analysis if long-term data show variability

No

1) Long-term data amenable to statistics and
2) Statistical analysis performed?

Yes

To both

If backed by statistical analysis and relevant supportive data:

Y = up to 1.5X, but not exceeding X + 6 months

No to 1) or 2)

If backed by relevant supportive data:

Y = up to X + 3 months

No

1) Long-term data amenable to statistics and
2) Statistical analysis performed?

Yes

To both

If backed by statistical analysis and relevant supportive data:

Y = up to 1.5X, but not exceeding X + 6 months

X = Period covered by long-term data

Y = Proposed retest period or shelf life
ICH Q1E Appendix A
Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products

Significant change at accelerated condition within 6 months?

- No
  - Long-term data show: 1) little or no change over time and 2) little or no variability?
    - No to 1) or 2) or both
      - Yes To both
        - Accelerated data show: 1) little or no change over time and 2) little or no variability?
          - No to 1) or 2) or both
            - Yes To both
              - Statistical analysis is normally unnecessary

- Yes
  - If backed by statistical analysis and relevant supportive data:
    - Y = up to 2X, but not exceeding X + 12 months

1) Long-term data amenable to statistics and
2) Statistical analysis performed?

- No to 1) or 2)
  - If backed by statistical analysis and relevant supportive data:
    - Y = up to 1.5X, but not exceeding X + 6 months

Y = Proposed retest period or shelf life
X = Period covered by long-term data

If backed by statistical analysis and relevant supportive data:
Y = up to 2X, but not exceeding X + 12 months
Approach

When a linear relationship is assumed, a regression analysis using a one or two sided 95% confidence interval can be used, as appropriate.

The shelf-life is established as the time point prior to the confidence limit intersecting the acceptance criterion.
Multiple batches / packages

Determine poolability of batches using ANOVA (analysis of variance) technique. Poolability tests to determine if the batches have common slopes and/or a common time-zero intercept. The test should be performed using a significance level of 0.25 for batch related terms and 0.05 for non-batch related terms.
Example: Assay
(expected to decrease with time)

Stability Shelf Life Application
(Final Model 1A)
Stability Analysis Variable: ASSAY

Estimated Shelf-life

Regression Line

95% Lower Confidence Interval

Lower acceptance criterion

Graph Produced by the SAS System (SAS V8.2, WIN_PRO) on 25 OCT 2006 at 10:46 AM
Example: Degradation Product

Stability Shelf Life Application
(Final Model 1A)
Stability Analysis Variable: TOT_DEG

95% Upper Confidence Interval  Regression Line

Upper acceptance criterion

Estimated Shelf-life

Graph produced by the GAO System (GAO V0.2, WIN_PLO) on 25Oct2000 at 16:50 AM
Current industry procedure for determining a proposed shelf life for a new drug product

- Assess “ICH Shelf Life” based on long term data, accelerated data and if applicable intermediate condition data against the ICH decision tree.
- Perform statistics if applicable.
- The proposed shelf life is then the shorter of the ICH decision tree shelf life and the shelf life estimated by statistical analysis.
ICH Decision tree shelf life
Passes 40°C/75%RH (6M) : 24 months
Or
Passes 30°C/65%RH (12M) : 18 months

Statistically estimated shelf life: 52.8 months
PQRI

- Product Quality Research Institute
  - Purpose
    “...serve as a forum for academia, industry and FDA to work cooperatively to conduct pharmaceutical product quality research and to support development of public standards ...”
  - Mission
    To advance science-based pharmaceutical product quality regulation.
PQRI Function

- PQRI advances science-based regulation, within the framework of risk management principles by:
  - conducting research and testing
  - collecting, analyzing and interpreting data
  - communicating results of its work to the public
- PQRI develops scientific consensus among regulatory authorities, industry and academia by:
  - providing a forum and process to discuss data and best practices, and to introduce important regulatory questions
  - sharing its research and recommendations through public presentations and publications
PQRI Strategic Direction

- shift from reacting to Regulatory Guidelines to trying to establish best practices for consideration by regulatory authorities
- embracing the FDA and ICH (Q8, 9 and 10) initiatives and aligning our scientific efforts to support
- extensive use of publications and workshops to stimulate more widespread discussion on important issues related to the quality of pharmaceuticals
- presents consensus recommendations to regulators and standard-setting bodies
Stability Shelf Life Working Group

- PQRI SSL WG
  - Working Group established in late 2006
  - members include statistical and pharmaceutical scientists from industry and academia
- Objectives
  - to propose best practices with respect to stability quality attributes
  - investigate statistical methods for estimating shelf life consistent with FDA Quality by Design (QbD) initiative
  - enhance pharmaceutical products through accurate estimation of shelf life
Stability Shelf Life Working Group

- Subgroups
  - CMC Subgroup
    - monitor progress of Working Group from CMC Development perspective
  - Statistical Subgroup
    - monitor progress of Working Group from statistical perspective
Stability and Shelf Life

The Working Group’s efforts are directed toward providing an alternative methodology for estimating shelf life which is robust to future batch release and consistent with the common understanding of shelf life.

The Working Group is currently finalizing a white paper with a working title of “CONSIDERATIONS FOR SETTING THE SHELF LIFE OF PHARMACEUTICALS”
Reconsideration of Shelf Life

- reconsideration of the definition of shelf life
  - focus on estimating shelf life as the parameter of interest
    - shelf life of the product
    - based on overall response of product
    - based on a percentage of units within specification
# Reconsideration of Shelf Life

- considering several options for estimating shelf life
  - “standard” approaches
    - random and fixed batches have been considered
    - confidence and prediction intervals on (overall) batch response
  - alternative approaches
    - quantile regression
    - calibration methods
    - tolerance interval estimates
    - interval estimates based on the distribution of interval estimates
PQRI Stability Shelf Life Working Group

David Christopher  Schering Plough Research Institute
Patrick Forenzo  Novartis Pharmaceuticals Corporation
Abhay Gupta  FDA / CDER
Paula Hudson  Eli Lilly and Company
Svetlana Lyapustina  Drinker Biddle & Reath LLP
Nate Patterson  Vertex Pharmaceuticals, Inc.
Michelle Quinlan  University of Nebraska-Lincoln
Dennis Sandell  S5 Consulting
James Schwenke  Boehringer Ingelheim Pharmaceuticals, Inc.
Walt Stroup  University of Nebraska-Lincoln
Dave Thomas  Johnson & Johnson
Terry Tougas  Boehringer Ingelheim Pharmaceuticals, Inc.
References:

ICH Q1A(R2) Stability Testing of New Drug Substances and Products

ICH Q1E Evaluation for Stability Data