PROVIDING VALUE IN PRODUCTS AND SERVICES THAT EMPOWER PEOPLE TO LEAD HEALTHIER LIVES.

Importance of Shelf Life Validation in Brand Integrity – What's on the Label is in the Bottle

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US Regulations for DS

- In theory, shelf life dating is entirely voluntary for manufacturers and packagers of dietary supplements. In addition, should a manufacturer or packager choose to implement shelf life dating the cGMP regulations themselves provide no guidance as to how the shelf life should be determined. However, in this 2007 preamble FDA makes a number of remarks on this subject, the first of which refers to the 2003 proposed cGMP rule:

US Regulations for DS

- "The preamble to the 2003 CGMP Proposal emphasized that, if you use an expiration date on a product, you should have data to support that date (68 FR12157 at 12204). We recommended that you have a written testing program designed to assess the stability characteristics of the dietary supplement, and that you use the results of the stability testing to determine appropriate storage conditions and expiration dates."

US Regulations for DS

- FDA's second statement (Preamble to the Final Rule) regarding data to support a product's shelf life is:
- "Because the final rule does not require that you establish an expiration date, we decline to offer guidance on the type of data that are acceptable to support an expiration date, other than to repeat that any expiration date that you place on a product label (including a "best if used by" date) should be supported by data."

Reality

- Requirements imposed by customers or by regulatory authorities in countries to which products are exported.
- Shelf life dates can minimize the company's liability since the use of a date indicates that the manufacturer is only responsible for requirements such as the quality, strength or potency, freedom from contamination, suitability for consumption, compliance with current regulations, etc. up until the stated shelf life date.

Assure Label Program

On the Label = In the Bottle

Factors Affecting Shelf Life

Chemical Stability

- Different dietary ingredients and supplements have differing degrees of inherent chemical stability, depending on their chemical makeup. Some kinds of molecules are very stable; they do not easily react with other molecules and will remain unchanged over long periods of time.
- Minerals (inert) such as silica or magnesium phosphate are quite stable, especially if kept away from moisture, and can remain unchanged over decades or longer.

Chemical Stability

- On the other hand, some kinds of molecules are less stable and react relatively quickly with other molecules to form degradation products.
- For example, unsaturated fatty acids such as EPA or DHA may oxidize over the course of a few months (or even less) when exposed to oxygen, especially if heat is present. These types of molecules may be described as “labile” or “reactive.”

Chemical Stability

- The inherent stability or reactivity of the chemicals present in a particular supplement can often be determined by the chemistry
- Additional information can be obtained through review of published literature, handbooks, or compendia; from vendors; or through stress testing or other testing

Microbiological Stability

- Different dietary ingredients and supplements have differing susceptibilities to microbiological growth.
- Excessive microbial growth may not only cause microbiological test results to exceed the specifications established for the product, but may also cause undesirable organoleptic and chemical changes (spoilage).

Microbiological Stability

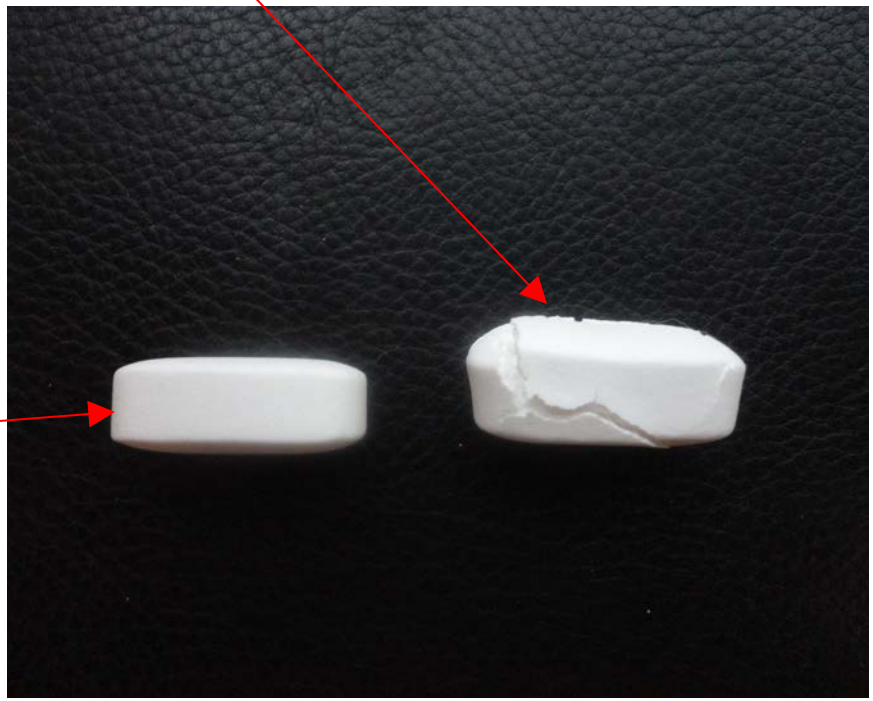
- No protein or carbohydrate are typically = no growth; minerals such as calcium carbonate or iron oxide are unlikely, by themselves, to grow bacteria or fungi.
- Low water activity or which contain high levels of salt or sugar, those which are highly acidic or alkaline (i.e. having a low pH or high pH), or which contain high levels of alcohol are also generally resistant to microbial growth.
- Materials which are derived from plant or animal sources, especially if they are hygroscopic (tending to absorb moisture from the air), are relatively likely to support microbial growth. In such cases, adequate shelf life may be obtained by suitably processing (steam) the material to reduce the level of microbes present, and/or by appropriate formulation, packaging, and/or storage to prevent microbes from multiplying to unacceptable levels.

Formulation

- The formulation of a dietary ingredient or supplement often has important effects on the shelf life. The most stable formulations are usually those which contain (and make label claims for) only inert materials, such as a trace minerals or calcium tablets.
- If any reactive materials (e.g. acids, bases, oxidants, or reductants) are included in a formulation, they will usually accelerate the degradation of other materials in the product. For example, multivitamin-mineral formulations often include a wide variety of chemicals, many of which can react with each other. Special steps may need to be taken to ensure adequate stability of these formulas, such as use of ingredients which are microencapsulated to isolate them from other ingredients.

L-Arginine 1000 mg Tablets disintegrated in humid climates, changed to stable form Arginine HCl

L-Arginine Base



L-Arginine HCl

Formulation

- Formulation overages are another means to ensure adequate shelf life. In this case, the product formulator will intentionally include more of a particular ingredient than is initially needed to meet label claim.
- Zinc
- Fat soluble Vitamins

Formulation

- Ingredients added to the formula for specific technical effects to lengthen shelf life.
- i.e. BHT, rosemary oil, or vitamins C or E may be added for their antioxidant effects; chelating agents such as EDTA may be added to bind reactive metal ions, thereby minimizing their degrading effects; and sorbate, benzoate, or other preservatives may be added to inhibit microbial growth.

Physical Form

- The physical form of a dietary ingredient or supplement can significantly affect the shelf life.
- Generally speaking, materials in solid form are more stable than in liquid form (all else being equal) because molecules in a liquid are able to move freely around and may thereby react with each other. In contrast, the molecules in a solid are less able to move around and interact, and are therefore less likely to chemically react with each other.

Physical Form

- The particle size of a solid also often affects its stability, especially for molecules which are sensitive to light, moisture, or oxygen.
- The smaller the particle size, the more surface area is exposed to the environment; this leads to more rapid degradation. In contrast, larger particles have less surface area and are therefore usually more stable.

Packaging and Storage

- Certain characteristics of a product's packaging can greatly affect shelf life. The container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapor transmission rate, oxygen permeation rate, and light transmittance or opacity all have important effects.
- In addition, any packaging components included inside the container, such as desiccants, rayon, or oxygen scavengers, may also affect the shelf life.

Packaging and Storage

- The packaging for each product should be chosen based on what is known about the stability of the material.
- For example, materials which are light sensitive should be packaged in opaque or dark containers, materials which are moisture sensitive should be packaged in moisture-proof containers and/or with desiccant packs, etc. Information to guide the choice of packaging may be found in the literature, recommended by the vendor, or derived from experience with stress tests or other testing of the product.

Shelf Life Tests/Examinations

Reference ICH Guidelines Q1A-Q1F

Shelf Life Tests/Examinations

- Companies should consider what types of tests are appropriate to establish each product's shelf life, and what criteria each such test should meet. Shelf life specifications should be established for those attributes which are susceptible to change during storage and which are likely to affect product quality, safety, and strength or potency.

Shelf Life Tests/Examinations

- The tests and examinations appropriate for any given dietary ingredient or supplement depends on factors such as:
  - The nature and specifications of the product;
  - The nature and specifications of its ingredients;
  - The product's label claims;
  - The product's packaging and storage conditions.

Shelf Life Tests/Examinations

- Acceptance criteria for a shelf life test may be different than those used for the same test during initial release of manufactured batches, especially where known changes are expected to occur during storage.

Shelf Life Tests/Examinations

- There are a wide variety of types of tests and examinations which may be relevant to establish shelf life:
  - Organoleptic testing
  - Physical attributes
  - Microbiological testing
  - Quantitative chemical tests
  - Impurity Tests

Shelf Life Tests/Examinations

- **<u>Organoleptic testing</u> -** Organoleptic tests compare the general appearance, color, odor, taste, and/or texture of aged product to those of freshly-made product. These tests are useful to evaluate whether the stored product will continue to be acceptable for use in production and/or to the consumer.

Physical Attributes

- Many physical characteristics play an important role in product quality and may be appropriate to monitor for changes during product storage.
  - Significant changes during storage in moisture content, loss on drying, water activity, and/or average dosage weight may indicate a problem. Where such changes are observed, further testing of chemical or microbiological attributes may be appropriate.
  - Disintegration and/or dissolution of tablets and capsules may change over time and may be appropriate to monitor during a shelf life study.
  - Tablets and capsules may also be monitored for changes in friability, hardness, and/or seal integrity, as applicable to the product.
  - Liquids and semi-solids may also be monitored for changes in viscosity, pH, clarity, precipitation, and/or phase separation, as applicable to the product. Powders may also be monitored for changes in for resuspendability, dissolvability, and/or caking, as applicable to the product.
  - It may be appropriate to monitor the package integrity of the container-closure system, especially where unusual seals or closures are used or where the packaging serves a special technical purpose.

Microbiological Testing

- The panel of microorganisms relevant to establishing a product's shelf life will depend on the type of product and the packaging.
- Shelf life specifications for many products typically include tests for total aerobic count and yeast and mold. However, other tests may be more suitable for certain types of products; for example, probiotic supplements may require testing the viable count of the species claimed on the label; products with a low pH may require testing for Lactobacillus acidophilus and/or other acidophiles ; and products packed in a low-oxygen environment may require testing for anaerobes.

Microbiological Testing

- Products whose water activity is too low to support microbial growth may not require microbiological testing at each time point; it may be sufficient to test at the beginning and end of the shelf life, if at all. For products susceptible to microbial growth, more frequent microbiological testing is recommended.

Microbiological Testing

- Generally speaking, testing for pathogens in materials which have been appropriately processed and are homogeneous need not be repeated throughout a product's shelf life, provided the batch was tested and found to be free of relevant pathogens at the time of manufacture.

Quantitative Chemical Tests (Strength)

- Where the content of a particular nutrient, phytochemical, or other chemically-defined component is claimed on the product label, shelf life testing should verify that the product maintains an appropriate level of that component throughout the labeled shelf life.

Quantitative Chemical Tests (Strength)

- FDA labeling law requires foods and dietary supplements to provide at least 100% of their claimed component levels throughout the shelf life

Quantitative Chemical Tests (Strength)

- In either case, the content of the claimed component may be determined at multiple time points throughout the product shelf life, using an appropriate chemical test method.
- However, in some cases such component testing may not be possible (e.g. in complex matrices where analytical methods of sufficient specificity and sensitivity are not readily available). Also, it may be unnecessary to test for every claimed component in a complex mixture; rather, it may be preferable to test for those components known to be less stable and to extrapolate those results to the components known to be more stable.

Quantitative Chemical Tests (Strength)

- Quantitative chemical tests may also be important for other ingredients such as microbial preservatives, antioxidants, or known degradation products.
- In addition, some companies may choose to monitor the content of known components in the formula as a guide to the product's stability, even when no quantitative label claims for those components are made on the product label.

Impurity Tests

- In general, it is not necessary for a shelf life specification to include tests for impurities such as heavy metals or pesticides, since these should not change so long as the product is stored properly
- However, there are some impurities whose content may change during storage and which may therefore be appropriate to be include in the shelf life study. For example, mycotoxin levels may increase during storage if elevated fungal counts are observed.

Stability Protocols

- Where a formal shelf life study is conducted, companies should consider writing a formal protocol or plan for the study. Such a stability protocol should describe, at a minimum:
  - The product(s) to which the protocol applies, including the packaging configuration(s).
  - The objectives of the shelf life study.
  - The number of batches of each product to be included in the study.
  - Sampling procedures to be used to obtain samples for the study.
  - Storage conditions for the study samples.
  - At what time points the study samples will be tested.

Stability Protocols

- Continued…
  - The test methods to be used.
  - Instructions for data handling and calculations.
  - Acceptance criteria for the data.
  - Specifications with which the product must comply.
  - Instructions for the documentation and evaluation of any deviations from the established protocol that may occur during the study.
  - Names, signatures, and dates of personnel approving the protocol for use.

Batch/Lot Selection

- The number and type of product batches to be included should be carefully considered. Typically 3 in pharma.
- On the other hand, for food shelf life studies, stress tests, photostability studies, and in-use testing, it is common to test just one batch.
- Batch(es) selected for testing should be at least pilot scale (manufactured using the same manufacturing procedure as full-scale production batches), made from the same ingredients as is usual for the product, and of comparable overall quality as is usual for the product
- Where multiple batches are tested, they should preferably be manufactured from different lots of ingredient. With regard to ingredients that are obtained from multiple vendors or sources, it may be appropriate to test one or more batches from each of these. It may also be appropriate to select additional batches for testing or study on an ongoing basis, either once per year or whenever a significant change occurs, such as a change in ingredient vendor or a change in manufacturing procedure.

Packaging

- The material used for shelf life testing or studies should be packaged in the same manner as is used for commercial storage and distribution of the ingredient or product (including the primary container closure system, the amount of fill inside the container, the label, and any secondary packaging).
- If this is not possible, the samples should be packaged with the same materials of construction as the commercial material is packaged in, and should be proportionately similar in terms of fill level and headspace.

Sampling

- The size and nature of samples to be pulled from each batch should be carefully considered. Where study samples are all pulled at the beginning of the study, the quantity must be sufficient to allow completion of all required testing over the course of as many time points as will be tested.
- On the other hand, where study samples are pulled from existing inventory at various time points, the quantity collected need be sufficient only for testing at the given time.

Sampling

- In general, stability samples should be pulled using proper sampling procedures to ensure the material collected is properly representative of the whole batch at the time of manufacture or receipt.
- In cases where samples from existing commercial inventory are pulled for shelf life testing, it may be appropriate to select samples from “worst case” conditions such as the warmest location in the warehouse.

Sampling

- The provenance of each sample used in the shelf life study should be carefully documented in case questions arise. This may include data such as the date of the sampling, the person who pulled the sample, the sampling SOP(s) used, the total size and number of containers in the batch at the time of sampling, the warehouse or other storage location(s) sampled (where applicable), the number and identity of batch containers from which sample portions were taken, the total size and number of containers in the sample, and whether the final sample represents a composite or grab sample.

Sample Storage Conditions

- Sample storage conditions.
- The chosen storage conditions should, at a minimum, be monitored and documented throughout the storage period; many companies go further and actively control the storage conditions, for example by use of environmental chambers which keep the storage environment within strict ranges of temperature and humidity.

Storage Conditions

- For real-time testing, the samples should be stored under conditions as similar as possible to those experienced by the product in commercial storage. Most commonly, this means storage at room temperature, i.e. around 25 °C (75 °F), and humidity between 30-70% RH. However, some companies conduct long-term testing at 30 °C ± 2 °C / 65% RH ± 5% RH.
- For materials intended to be stored and distributed under refrigerated or frozen conditions, the shelf life conditions should be adjusted accordingly; for example in the drug industry, real time refrigerated studies are typically conducted at 5 °C ± 3 °C while real time frozen studies are typically conducted at -20 °C ± 5 °C.

Accelerated Conditions

- For accelerated testing, samples are typically stored at either 30 °C ± 2 °C / 65% RH ± 5% RH and/or at 40 °C ± 2 °C / 75% RH ± 5% RH. Accelerated testing of refrigerated materials is typically conducted at 25 °C ± 2 °C / 60% RH ± 5% RH. Accelerated testing of frozen materials may be conducted at 5 °C ± 3 °C or at 25 °C ± 2 °C.
- Companies may use other conditions where justified.

Test Frequency

- The time points at which shelf life testing will be performed depend on the type of study and the intended shelf life of the material.

Test Frequency

- For real time studies of materials with long shelf lives (longer than 1 year), testing is generally performed at least at the beginning (T = 0) and end of the shelf life. In addition, it is common in the drug industry to test every 3 months throughout the first year (T = 3, 6, 9, and 12 months), every 6 months during the second year (T = 18 and 24 months), and annually thereafter until the end of the shelf life.
- For accelerated studies, testing is generally performed at the beginning, middle, and end of a 6-month study (T = 0, 3, and 6 months).

Test Frequency

- If experience or other information indicates a significant change may occur in the material during the shelf life testing, it is often wise to add additional time points for testing.
- Conversely, if experience or other information indicates that no significant change is likely to occur in the material during the shelf life testing, it is justified to use fewer time points for testing.

Test Frequency

- Where a significant change occurs in the material during the shelf life testing, such that the material fails to meet the established specifications, it is generally not necessary to continue the testing or study.
- Where no significant change is observed during the testing or study, it may be possible to extend the shelf life of the material beyond what was originally expected.

Bracketing

- Where a company has several products which are identical except for (a) strength or (b) container size or fill, it is generally not necessary to test the shelf life of every configuration.
- Bracketed shelf life study may be used, in which only the extremes of each factor are tested.
- Bracketing is not generally advisable where different dietary ingredients or different excipients are used among different versions of the formula.

Bracketing

- If the stability of the extreme cases prove to be different from each other, the shelf life of the intermediate cases should be considered no more stable than the least stable extreme case.

Matrixing

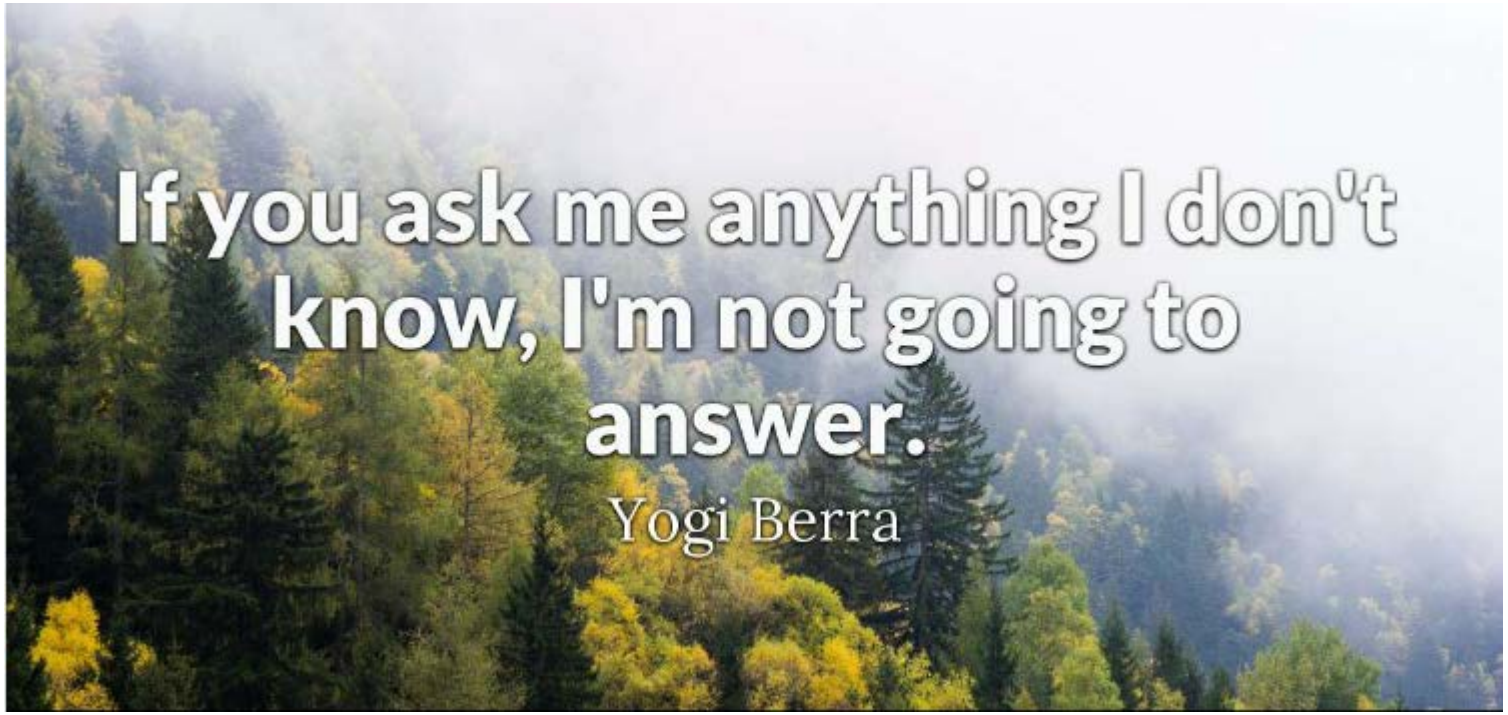
- Matrixing can be useful for shelf life testing where a company has numerous variations of a formula.
- In a matrixed shelf life study, a selected subset of the variants is tested for one attribute at one time point; at the next subsequent time point, a different subset is tested for the same attribute, and so on throughout the study.
- This study design assumes that the stability of each subset of samples tested is representative of all the samples at that time point.

Matrixing

- Matrixing can be applied to design factors such as:
  - Different strengths or potencies with identical or closely related formulations.
  - Different container sizes and/or fills in the same container closure system.
  - Different container closure systems if it can be shown that relative moisture and oxygen transmission rates remain similar.
  - Different batches made using the same process and equipment.

Matrixing

- Matrixing should generally not be performed across different test attributes or across different storage conditions.
- The matrixing design should be as balanced as possible so that each combination of factors is tested equally over the duration of the study. All selected factor combinations are usually tested at the initial and final time points, while only a subset of the combinations is tested at each intermediate time point.
- Due to the reduced amount of data collected, a matrixing shelf life study has less precision and yields a shorter shelf life than the corresponding full study.
- Furthermore, a matrixing design should be used only where experience or other information indicates that the shelf life of the product is predictable. If there is uncertainty or variability, a full study is generally preferable.


If you ask me anything I don't know, I'm not going to answer.
Yogi Berra