

Stability/BUDs: Science and Guidance: Part I

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Outline

- Requirements for current good manufacturing practice (CGMP)
- How the draft guidance describes a risk-based approach for stability/BUDs

Requirements for CGMPs

OFs must comply with CGMP requirements

- Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if “the methods used in, or the facilities or controls used for, its manufacture, processing, or holding do not conform to or are not operated or administered in conformity with [CGMP]”
- Under section 503B(b)(4)(B) of the FD&C Act, OFs are inspected by FDA according to a risk-based schedule

Requirements for CGMPs

- FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211
- FDA intends to promulgate more specific CGMP regulations for OFs
- Until these final regulations are promulgated
 - OFs are subject to the CGMP requirements in 21 CFR parts 210 and 211
 - Revised **draft** guidance provides for proposed policies under which FDA generally does not intend to take regulatory action against an OF regarding certain CGMP requirements during this interim period.

Draft Guidance Describes a Risk-Based Approach

- Draft guidance represents FDA's intent to recognize the differences between outsourcing facilities and conventional drug manufacturers, while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.

CGMP Requirement for Stability Program

- A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (21 CFR 211.166)
- An expiration date is established through the conduct of a stability program that includes testing to assess the product's performance against specifications after aging to the desired expiration date (21 CFR 211.137)

Stability Studies

- The conditions outlined in ICH guidance for industry Q1A(R2) Stability Testing of New Drug Substances and Products are recommended
- Proposed policies describe a risk-based approach that recognizes that a compounded drug's batch size may be small and the frequency of batch production may vary considerably

Stability Studies

- Under 211.122, 211.160, and 211.166, procedures established for assessing the stability of drug products compounded by OFs must achieve the following:
 - Incorporate stability-indicating test methods that are reliable, meaningful, and specific
 - Evaluate samples of the drug product in the same container-closure system and with the same or representative label and adhesive that will be affixed to the container in which the drug product is marketed

Stability Studies (continued)

- Evaluate samples for stability that are representative of the batch from which they were obtained and are stored under suitable conditions.
- Incorporate testing to evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

Proposed Enforcement Discretion Policies

- FDA's revised draft guidance on CGMP for OFs sets forth proposed policies under which FDA generally would not intend to take regulatory action against an OF regarding certain CGMP requirements in parts 210 and 211 until more specific CGMP regulations for OFs are promulgated. The following slides summarize the proposed enforcement discretion policies concerning stability testing stated in the revised draft guidance.

Proposed Enforcement Discretion Policies

- FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing requirements if all of the following apply:
 - Drug product is compounded solely by combining two or more drug products approved under section 505 of the FD&C Act
 - Approved drug product labeling of at least one of the components specifies how to assign an in-use time
 - Compounded drug product has been prepared and labeled with an in-use time in accordance with the approved product labeling
 - In-use time is used as the expiration date (if in-use time does not exceed the expiration date of any of the approved drug products). If two or more approved drug products with in-use times are used, the shortest in-use time is used as the₁₁ expiration date for the compounded drug product

Proposed Enforcement Discretion Policies

- Taking into account the unique aspects of compounding, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the Stability section and in Appendix B of the draft guidance, such as using a BUD established through limited stability testing or, for certain lower risk situations, using a default BUD as the expiration date in lieu of establishing an expiration date through the conduct of a full stability program required under part 211 . . .

Proposed Enforcement Discretion Policies

- . . . If the following apply:
 - Compounded drug's BUD does not exceed appropriately established expiration or retest-by dates for any components used
 - If the drug is compounded from an approved drug product, and the approved product labeling recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months), but also provides for storage at another condition (e.g., stable at room temperature for up to 14 days), the compounded drug product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD of the compounded drug does not exceed 14 days for room temperature)

Proposed Enforcement Discretion Policies

- For repackaged products, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the Stability section and in Appendix B of the draft guidance, if:
 - (1) the BUD does not exceed the expiration date of the drug product that is being repackaged; and
 - (2) if the approved product labeling for the drug product being repackaged recommends one type of storage but also provides for storage at another condition, the repackaged product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling

Proposed Enforcement Discretion Policies

- The two studies below are required to be completed before a batch is released (see §§ 211.166, 211.167)
 - Container-closure integrity testing is conducted on samples aged to or beyond the desired BUD or expiration date to ensure that sterility is maintained over that time period
 - Antimicrobial effectiveness testing for drug products labeled or intended to be multiple dose is conducted on samples aged to the proposed BUD or expiration date (Note that antimicrobial effectiveness testing is container-closure specific)
- Each study only needs to be conducted once for each formulation and container-closure system

Proposed Enforcement Discretion Policies

Table 2. BUDs for Non-Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
≤5,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
>5,000 units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

Default BUDs (Non-Sterile)

Table C: Default BUDs for Non-Sterile Drug Products With Aggregate Batch Size $\leq 5,000$ Units

Type of Product	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)
Solid dosage forms	180 days	N/A
Water activity >0.6	Preserved: 30 days Unpreserved: Not applicable	Preserved: 30 days Unpreserved: 14 days
Water activity ≤ 0.6	90 days	N/A

Proposed Enforcement Discretion Policies

Table 3. BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
≤1,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
>1,000 units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

Default BUDs (Sterile)

Table D. Default BUDs for Aggregate Batch Size $\leq 1,000$ Units With Given Processing and Storage Conditions

Processing Conditions	Contains a Preservative?	Storage Conditions		
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
<ul style="list-style-type: none"> Finished drug product is aseptically processed; and A sterility test has not been completed before release 	No	6 days	9 days	45 days
	Yes	28 days	42 days	45 days

Default BUDs (Sterile)

Processing Conditions	Contains a Preservative?	Storage Conditions		
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
<ul style="list-style-type: none"> Finished drug product is terminally sterilized; A validated sterilization cycle that uses physical, chemical, or biological indicators is employed; and A sterility test has not been completed before release 	No	14 days	28 days	45 days
	Yes	28 days	42 days	45 days
<ul style="list-style-type: none"> Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release 	No	28 days	42 days	45 days
	Yes	42 days	42 days	45 days

Proposed Enforcement Discretion Policies

- Conditions in Appendix B: Default BUD (No Testing) for **Non-Sterile** Drug Products: Aggregate Batch Size $\leq 5,000$ Units
 - (1) a BUD has been assigned according to Table C;
 - (2) water activity testing is conducted as described, if applicable, to determine the type of product for assigning the BUD;
 - (3) literature or other scientific information, including relevant commercially available product labeling for a similar drug, does not indicate that the drug product may not be physicochemically stable over the time period listed; and
 - (4) the BUD is used as the expiration date

Proposed Enforcement Discretion Policies

- Conditions in Appendix B: Default BUD (No Testing) for **Sterile** Drug Products: Aggregate Batch Size $\leq 1,000$ Units
 - (1) a BUD has been assigned according to the criteria based on processing conditions in Table D;
 - (2) literature or other scientific information, including relevant commercially available product labeling for a similar drug, does not indicate that the drug product may not be physicochemically stable over the time period listed; and
 - (3) the BUD is used as the expiration date

Proposed Enforcement Discretion Policies

- **Limited Stability Testing:** FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing and expiration date requirements if the outsourcing facility uses the approach outlined below describing a number of lots and a set of tests—which should be conducted at lot release as part of normal operations—to be performed at the time of the desired BUD. This does not apply to non-sterile unpreserved aqueous drug products because of the higher risk of microbiological proliferation.

Proposed Enforcement Discretion Policies

- **Limited Stability Testing:** The following conditions apply:
 - Samples are evaluated following aging under the long-term storage conditions (i.e., temperature and humidity) in ICH Q1A(R2)
 - The data from each time point are evaluated against the established specifications for the compounded drug product.
 - The BUD is not longer than 12 months
 - If the data for any test fall outside of the established specifications, the BUD is restricted to the last time point at which the data remained within specifications, or the default BUD (slides 16, 18, and 19) is used

Proposed Enforcement Discretion Policies

Limited Stability testing (continued):

- FDA strongly recommends the inclusion of testing at at least one interim time point
- If the data at the final time point do not confirm the stability of the product at the desired BUD, but the data at the interim time point are acceptable, a BUD equal to the interim time point meets the second condition
- Samples from one lot are tested
- Each unit subjected to one or more tests that compromise the integrity of the primary container-closure is only tested at a single time point

Limited Stability Studies - Tests to be Conducted

Non-Sterile

- Appearance.
- pH, if applicable (e.g., for aqueous formulations).
- Assay
- Appropriate specifications
- Microbiological tests, if water activity >0.6

Sterile

- Appearance.
- Color and clarity.
- Visible particulates.
- pH, if applicable (e.g., for aqueous formulations).
- Assay
- Subvisible particles (10 μm –100 μm)
- Sterility or container-closure integrity tests

Stability/BUDs: Science and Guidance: Part II

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Outline

- Reminder
- Defining Stability Indicating
- Stability Program Goals
- Enemies and Allies of Stability
- Stability Time Points
- Stability testing in cases of multiple “strengths”
- Discussion of Selected Specific Tests

Reminder: Stability Studies

- Drug product samples in the same container-closure system and with the same label and adhesive as marketed
- Samples are representative of the batch from which they were obtained and which were also stored under labeled storage conditions.
- Stability-indicating test methods
- Evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

What Does Stability Indicating Mean?

- A Stability-indicating method for a drug product may be defined as
 - a validated quantitative analytical method that can detect and appropriately quantify the change over time in the chemical, physical or microbiological properties of the drug product, and
 - which is specific so that the content of active ingredient(s) and relevant degradation products can be accurately measured without interference.
 - Requirements per 21 CFR 211.166(a)(3)
 - More details here:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4830733/>

Goals of A Drug Product Stability Program

- Support that the drug product* will perform the same at end of expiry (beyond default BUD) as it does at release
 - In terms of safety, efficacy, and quality
 - Risk based assessment and testing process
- Support any investigative and/or corrective actions in the event of problems
 - Including any reserve samples as indicated in the draft guidance

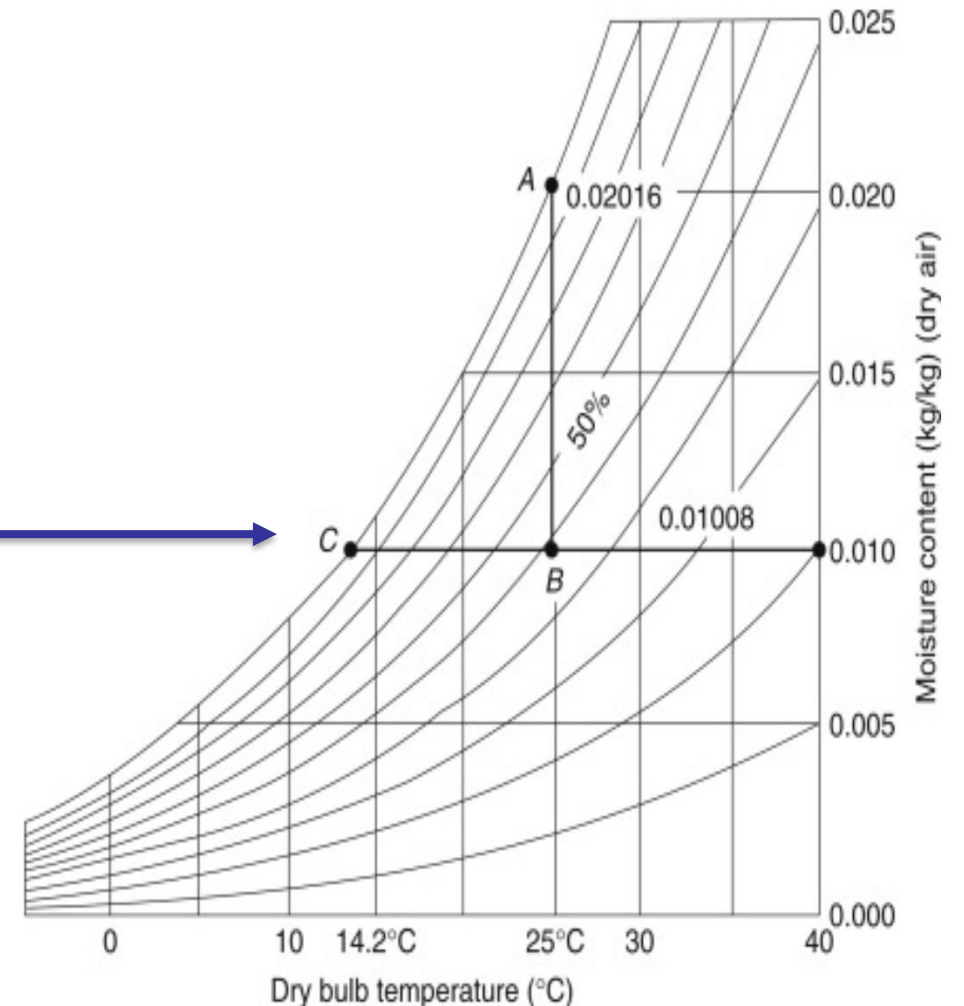
****Drug product includes the formulation, container closure and primary container label in the form that it is distributed.***

Enemies of Drug Product Stability

- Heat
 - Storage temperature (T)
- Moisture
 - Storage humidity as percent relative humidity (%RH)
- Light
 - Controlled by packaging and administration handling
- Oxygen
 - Can be eliminated during manufacture
 - Will find a way back into the product
- Time

%RH and Temperature

- **%RH** is the percent of water vapor saturation in air at a specified temperature
- Cooling e.g., from 25°C / 50%RH to 13°C, doubles the %RH from 50%RH to 100%RH.
- Continued cooling may condense water from the headspace directly into/onto the formulation.



Allies of Drug Product Stability

- Quality ingredients
 - Purity and potency control start here
- Appropriate Compounding operations
 - Limit introduction of foreign matter
 - Limit degradation induced by processing conditions
- Packaging / container closure
 - A key factor in maintain product integrity
 - Controls ingress (or loss) of moisture
 - Controls ingress of oxygen
 - Can protect from light
 - Physical protection of the formulation inside

Stability Program Time Points to Justify Longer Than Default BUDs

- Release testing counts as time zero
- Testing only at expiry leverages all risk at time zero.
- A stability testing time point midway to planned expiry provides a backup position
- Provides some information regarding trends
- Allows for proactive action before going OOS in some cases.

Stability Program for Multiple Strengths of the Same Formulation

- "Strength" here includes different API concentrations and presentations as follows
 - Concentration of API (liquids and semisolids) in the formulation
 - Volume fill of formulation (liquids and semisolids) in the same container type (headspace : formulation ratio should be considered)
 - Tablet or capsule API content per unit for proportional formulations only
 - Different numbers of units of tablets or capsules in the same container type (e.g., bottles of 10 versus 100 capsules)

Stability Program for Multiple Strengths of the Same Formulation

- If 3 or 4 drug product strengths, concentrations, volume, or count presentations are produced, test the high and low extremes (e.g., if available strengths include 2.0 mg/mL, 3.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL, test 2.0 mg/mL and 10.0 mg/mL).
- If 5-10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 1 intermediate case.
- If more than 10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 2 intermediate cases.

Stability Program for Multiple Strengths of the Same Formulation

- In this example, volume fill varies for the same formulation.
- Container closure is of the same type and materials
- The 5 mL and 50 mL must be tested on stability.
- Of the remaining intermediate fills, which one is the highest risk re stability?

(F) Fill Volume (mL)	Container size (mL)	H Head space (mL)	H/F ratio
5	20	15	3
8	20	12	1.5
10	20	10	1.0
15	20	5	0.3
20	60	40	2.0
30	60	30	1.0
50	60	10	0.2

A More Complex Example of Bracketing with Matrixing for Stability Studies

- The hypothetical drug product comes in four concentration strengths 2 mg/mL, 4 mg/mL, 6 mg/mL and 8 mg/mL and all contain the **same inactive ingredients**
- Each strength comes in four volume presentations; 5 mL, 10 mL, 15 mL and 20 mL
- The 5 mL and 10 mL are in 15 mL containers
- The 15 mL and 20 mL are in 30 mL containers
- The container closure is the **same type and material** in all cases
- **What presentations should be studied on stability?**

Matrixing with Bracketing Stability Study Example

What's an **appropriate minimum** number of studies in this case

- From the Table, there are 16 cases (i.e., products) confounded with two container sizes (15 mL and 30 mL)
- The **extrema** (corners) of the 16 possibilities should be tested
- The additional **two studies** for intermediate testing ensure all 4 strengths, all 4 volumes and both container sizes are rationally covered in 6 total studies.

API %	H/F for 5 mL fill in 15 mL vial	H/F for 10 mL fill in 15 mL vial	H/F for 15 mL fill in 30 mL vial	H/F for 20 mL fill in 30 mL vial
2	2	0.5	2	0.5
4	2	0.5	2	0.5
6	2	0.5	2	0.5
8	2	0.5	2	0.5

Brief Discussion of Selected Specific Tests

At Release and on Stability per Guidance

- Identity (not necessary on stability)
- Applicable USP criteria (applies to release and stability case by case)
- Strength or Assay
- Purity
- Appearance including color and clarity
- pH if applicable
- Capsule / tablet disintegration as applicable
- For heterogenous dosage forms; content uniformity in certain limited instances
- Non-sterile microbial testing
- For sterile products limits on particulates per USP <788>, <789>, and <790>
 - Visible
 - Subvisible (10 *um* to 100 *um*)

Assay and Purity on Stability

- **Strength or Assay**
 - as % of label claim
 - Usually by HPLC against a reference standard using validated method
 - Validated methods are specific, accurate, precise, robust, and are reproducible (day to day and operator to operator, etc.).
- **Purity**
 - Non-API peaks should not increase beyond specifications (e.g., by relative peak area to parent API peak area)
 - Non-API peaks that increase on stability may be degradants or leachables

Appearance on Stability

- Appearance including color and clarity
 - The formulation appearance should be within acceptable release ranges regarding color, clarity, surface appearance, etc.
 - As relevant assess; phase separation / creaming for creams and other emulsions and sedimentation quality (e.g., flocculated/deflocculated) for suspensions
 - Discolored, faded, or detached labels are failures
 - Leaking container closure is a failure.
 - Note: inks, adhesives and other label constituents (e.g., vanillin in paper made from ponderosa pine) can migrate through semipermeable containers

pH on Stability

- pH as applicable
 - Suitable for aqueous based solutions
 - Also suitable for colloids, suspensions, and emulsions where that measurement is relevant to safety, efficacy, or quality
 - The drug product should be within the target pH range for the entire shelf life
 - Watch for trends that come close to pH range limits
 - May signal degradation or some other physicochemical change going on

Tablet / Capsule Disintegration on Stability

- For immediate release tablets and capsules
 - Time to disintegration should be within release range
 - USP <701> apparatus and method
 - Test 6 (all 6 must pass) or 18 units (16/18 must pass)
- If modified release tablet / capsule more dissolution testing and criteria are necessary at release and on stability

Rationale for Limited Within Unit Content Uniformity (CU) Testing on Stability

- CU issues for **suspensions, and emulsions**
 - Changes in droplet or particle size along with re-suspendability changes (suspensions) or phase separation (emulsions) over time, suggest that within container content uniformity testing may be advisable on stability **in multiple dose presentations**.
- Test for drug content / concentration at top and bottom of the product after labeled instructions for “shaking” are followed.
 - Will detect changes in suspension or emulsion performance not visible by assay of the entire contents at once

Limited Within-Unit CU Testing on Stability

- Factors elevating within unit CU risk for heterogenous dosage forms
 - Narrow therapeutic index
 - Number of individual doses per container
 - Low drug load as percent of total formulation
 - Errors in mixing/de-mixing are magnified for solid systems
 - Complex compounding operation(s)
 - Milling (e.g., particle size reduction)
 - Mixing / blending solids
 - Emulsification processes

Limited Within-Unit CU Testing on Stability

- Statistically relevant sample sizes may be hard to determine
 - Mean and standard deviation (with limits on each) start making sense around $n=10$
 - E.g., 5 bottles of suspension for content top and bottom
 - This may be problematic near the 60 unit batch size aggregate threshold.

Thank You

Questions?