FDA/CDER SBIA REdI Generic Drug Forum 2019

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STABILITY CASE STUDIES

DIFFERENCES FROM ICH Q1 A-E for ANDAs

- **6** months of LT stability data for 3 **pilot** batches as opposed to **12** months for NDAs
- Dosage form specific batch size recommendations and a definition for small scale batch for ANDAs

Application Processing

- Submission Evaluation – Multistage process
- Preliminary Evaluation of Content - a substantially complete application
- Detailed Evaluation of Content – technical and scientific adequacy

Application Content

- An ANDA is a proposal to market a generic drug product.
- It contains sufficient information to support that statutory and regulatory requirements are met.
- Sufficient information allows a substantive review regarding adequacy of the application.

Application Content

- Application not substantially complete
- Cannot perform a detailed evaluation of content
- Refuse to Receive

Stability

- Stability is one topic evaluated for adequacy of the application
- Information is used to determine expiration dating period, maintaining safety and quality
- Several factors contribute to the adequacy of the stability information

Stability Input

- Stability profile determines expiration dating period, maintaining appropriate quality and safety
- Stability study protocols, including product orientation
- Sample sources, including certain manufacturing issues such as scale, reproducibility, component variability.

Preliminary Evaluation of Content

- Statute
- Regulation
- Guidance

Guidance

- ICH Q1A, Q1B, Q1C, Q1D, Q1E Harmonized Tripartite Guidelines
- ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers

Refuse to Receive

- Does not involve a detailed discipline-specific evaluation
- RTR generally based on absence, without justification, of specific recommended information

Audience Question

The most frequent reason for a stability related Refuse to Receive (RTR) deficiency is:

A. Failing to use 2 API lots for each strength

B. Failing to submit 180 days of stability data

C. Failing to provide stability data for multiple orientations for liquid products without sufficient justification

D. Failing to submit stability data with 3 time points

Stability related RTR decisions

	FY 2015		FY 2016		FY 2017		FY 2018	
	No.	%	No.	%	No.	%	No.	%
Missing 3 time points	3	7.7 %	5	6.4 %	1	1.8%	1	3.6%
Missing 2 API lots	11	28.2 %	14	18%	7	12.3%	7	17.9%
Lack of 3 or 6 month data	16	41.0 %	50	64.1 %	47	82.4%	17	60.7%
*Misc.	9	23.1%	9	11.5 %	2	3.5%	3	10.7%
TOTAL STABILITY RTRs	39	28.7%	78	33%	57	30.6%	28	29.7%
TOTAL OVERALL RTRs	136	---	237	---	186	---	94	---

***Misc = Missing or incomplete data, inadequate bracketing, orientation issues, missing pull dates & batches**

Top Stability RTR issues

- Failing to use 2 API lots **for each strength**
- Failing to submit 180 days of data (ACC and/or LT) with 3 time points and INT with 2 time points.
- Failing to provide INT data on all 3 batches, if ACC data fails
- Failing to provide the full 6 months (180 **consecutive** days) worth of failed ACC data
- Failing to provide stability data for multiple orientations for liquid products without sufficient justification

Data Recommendations

- Need for minimum 2 API lots
- Use of multiple orientations
- Submission of 6 months of ACC study data even if there's a failure at any point

CASE STUDIES: Stability RTR Major Deficiency

Case Study 1

The stability data provided in your submission is incomplete. You have failed to provide 6 months of INT data for batch A.

Case Study 2

You have used only 1 DS lot to manufacture the 3 primary batches of X strength. A minimum of 2 drug substance lots should be used to prepare the 3 primary batches of each strength of DP.

Identification of Different API lots

Strength	Primary Batch Number	Drug Substance Batch Numbers	
		Drug Product (DP) Manufacturer Batch Number	Drug Substance (DS) Batch Number
Strength 1	Exhibit Batch A001	DP API Lot 1	DS Lot 1
	Exhibit Batch A002	DP API Lot 2	DS Lot 2
	Exhibit Batch A003	DP API Lot 3	DS Lot 3
Strength 2	Exhibit Batch B001	DP API Lot 1	DS Lot 1
	Exhibit Batch B002	DP API Lot 2	DS Lot 2
	Exhibit Batch B003	DP API Lot 3	DS Lot 3
Strength 3	Exhibit Batch C001	DP API Lot 1	DS Lot 1
	Exhibit Batch C002	DP API Lot 2	DS Lot 2
	Exhibit Batch C003	DP API Lot 3	DS Lot 3

Case Study 3

You have failed to provide 6 months (180 days) of **ACC** data. The initiation date of **September 22, 2017** for batch X, together with the latest pull date of **March 15, 2018** does not cover the recommended 6-month (180 day) min. hold time.

Adds up to 175 days. The correct acceptable latest pull date could be March 20, 2018 (175+5 = 180 days)

Case Study 4

Your ACC studies for **all** of your submission batches, should cover a min. period of 6 months. While you have provided at least 6 months of *INT.* data, you should also provide **ACC** data for each submission batch covering a period of no less than 6 months.

Case Study 5

You have failed to provide 6 months of upright INT stability data for all submission batches for X strength. You have provided INT data for the batches that showed significant changes in the acc. conditions. If ACC data show a significant change or failure of any attribute in 1 or more batches, an applicant should submit INT data for all 3 batches.

Alternate Approaches to avoid RTR

- Inclusion of a justification in the submission
- Use of response to a controlled correspondence

CASE STUDIES: Proposed Approaches

Case Study 1

Applicant submits data less than 180 days. However, they provide LT data in support of their expiration dating period (i.e., propose 24 month expiration, based on 24 months of LT data).

Case Study 2

Applicant did not provide 180 days of data because their product could not be tested due to melted capsules, melted suppositories, or leaky bottles. (Applicant did provide 180 days of INT and LT data.) May need additional justification.

Additional Recommendations

- Provide and verify start dates and pull dates to ensure that the amount of stability data meets the recommendations
- Verify that all stability data for all batches has been provided i.e. avoid duplicate and missing data
- Check for consistency in lot numbers between stability data and exhibit batch manufacturing records

THANK YOU!


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