ANDAs: Stability Testing of Drug Substances and Products-Industry Perspective

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Disclaimer

• This presentation contains a summary of the opinion and perspective from GPhA member industry representatives on the topic of ANDAs: Stability Testing of Drug Substances and Products- Industry Perspective.

• This presentation does not necessarily represent the opinion of the presenter nor its employers.
Industry Thanks OGD Team For Considering our request to move the implementation date to one year from the date of the final guidance date.
Issues Covered

• Impact of the implementation of the Guidance
• Stability Q&A document High level Overview
• Areas of Clarification
• Future considerations
Impact of the implementation of the guidance

- The new stability requirements represent significant changes for industry and time/resources required to fully implement.
  - Cost of generic drug development increased at a minimum-1.5 fold but based on API costs could be much higher
  - Timelines of development increased by 2 fold
  - It is projected that the workload in stability labs for the enhanced stability testing will increase by 45% over 3 years
  - Firms stability study budget will increase by 40% over 5 years
Stability Q&A Guidance overview

**Scope and Requirements**

- Implementation date of June 20, 2014.
  - NO EXCEPTIONS
- Stability data from 3 three pilot scale batches or two pilot scale batches and one small scale batch batches needed at the time of submission
- Stability data at the time of ANDA submission is 6 months of ACC and LT. 6 months of INT recommended
- Significant change at 6 month ACC for 1 or more batches to be supported by Intermediate data for all 3 batches

**Data Review**

- ICH Q1E principles will help in the calculation of expiration dating.
- FDA will grant a proposed expiry period of two times the available long-term data at the time of approval (up to 24 months)
- Agency expects 6 month of data. 24 weeks of data not acceptable
- Applicants to update with 12 months of stability data post submission

**Drug Master File**

- ICH Q1A(R2) three primary batches (at least of the pilot scale size) for the drug substance filed in the DMF.
- Minimum of 6 months of accelerated and 6 months of long-term data for the pilot scale batches to be submitted initially
- To pass the Completeness Assessment initial and one additional time point for the accelerated studies and long-term studies are sufficient.
Stability Q&A Guidance overview

**DP Mfg and Pkg**
- Split filling one batch of bulk solution into different fill volume sizes does not constitute discrete batches.
- Where applicable, secondary packaging is to be included for all three batches.
- All three batches to be packaged in the container closure system proposed for marketing.

**DP Mfg and Pkg**
- A minimum of two lots of the drug substance should be used to prepare the three primary batches of drug product.
- Regardless of the dosage form, the 6 months of data from 3 discrete batches is the requirement.
- Pathway provided for introduction of alternate API source with reduced stability testing.

**Dosage form Specific mfg and pkg recommendation**
- Oral Dosage form
- Parenteral Dosage form
- Transdermal
- Topical
- Guidance provides exception where in the submission ANDA batch can have smaller size than the plot scale.
Stability Q&A Guidance overview

**DP Mfg and Pkg**
- All the ANDA submission batches to be manufactured under cGMP requirements
- The specification to be the same for all three batches.
- All the batches for submission need to be produced at the same site

**Pathway to reduced stability testing for dose proportional formulations manufactured from common blend**
- Guidance does not apply to amendment pending ANDA
- All three batches should have the same composition

**Stability Studies**
- Agency expects four time points. 0, 3, 6 and one additional point.
- For applicable products primary batches should be placed in inverted and upright position
- PET test and Preservative content one of the Primary batch
High Notes on FDA STABILITY Q&A GUIDANCE

• The responses have clarified Agency’s expectation on many areas in relation to stability testing
• The granularity of responses for many of the questions enables the industry to plan its activities
• The effort of the stability working group is much appreciated
### Request for further clarification on

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<thead>
<tr>
<th>Intermediate Stability data</th>
<th>Bracketing and Matrixing</th>
<th>Expiration dating/Storage of Batches</th>
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<td>• Clarity needed if firms can submit with 6 Mo ACC and 6 Mo CRT and 3 Mo INT. This is specific to scenarios where the INT stability was started upon looking at the ACC stability failure.</td>
<td>• In the instanceAgency does not agree with the firms matrixing and bracketing design at the time of screening, we request agency allow the firms to provide a commitment to revise the stability protocol.</td>
<td>• Please clarify Agency’s expectation/requirement of long term data without variability</td>
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<td>• In specific instances if drug product is not stable in ACC conditions can firms submit 6 months of INT and CRT data at submission</td>
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Request for further clarification on Drug Product Manufacturing and Packaging

- Use of equipment of similar design and operating principles meet the conditions of definition of “primary batches” (B.2.2.3 selection of batches Q1R2). Therefore please clarify if it is acceptable to package the smaller batch using the equipment of same design and operating principles as the equipment used to package the pilot scale batches.

- Clarify if this 50L batch size requirement does not apply if the submission batch and the proposed commercial batch are of the same size.

- For Transdermal products, Please clarify if the 10% proposed maximum size commercial batch is based off of finished packed units or the bulk matrix laminate.
Request for further clarification on

Drug Product Manufacturing and Packaging

• Clarify that if small scale batches are produced for submission in a separate R and D pilot area in the same facility that mimics operations in the commercial area satisfies FDA's expectation that all batches must be produced at the same site.

• Can agency confirm that a 10% commercial scale batch size is based off of the bulk pre-filled cream/lotion/gel batch. We concur with agency’s packaging representative samples from all three batches.
Future consideration's

• GPhA requests Agency's reconsideration on the requirement of fourth time point for conducting stability studies. The requirement of the fourth time point is inconsistent with ICH or requirements of any other highly regulated region.

• GPhA proposes for Agency’s consideration on a pathway to addition of alternate manufacturing site. GPhA proposes a pathway for addition of alternate manufacturing site by manufacturing one of the pilot scale batches at the alternate site.

• Generic Industry requests the Agency to keep this Q&A document as dynamic and to be updated periodically as Agency becomes aware of new issues.

• GPhA believes there is an opportunity to discuss on Prior Approval Supplement relief due to additional data provided in the ANDA in combination with QbD information.
Future consideration's

• GPhA request Agency’s comment on the impact of the additional data submitted on the review timelines.

• With the advent of QbD principles in the generic drug development GPhA believes there are further opportunities for flexibility and dialogue as it relates to agency’s Stability expectation.

• GPhA also requests the Agency to setup a dedicated OGD @stability email box to enable industry to communicate with agency for stability related specific queries.