



October 11, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Comments of the Generic Pharmaceutical Association for Docket No. FDA-2012-D-0938-0027: Draft Guidance for Industry; Availability: Abbreviated New Drug Applications; Stability Testing of Drug Substances and Products, Questions and Answers.

The Generic Pharmaceutical Association (GPhA) acknowledges the efforts of the FDA on **Docket Number FDA-2012-D-0938-0027, in response to an FDA call for comments concerning Stability Testing of Drug Substances and Products.** We would also like to thank you for giving us the opportunity to share our thoughts on this important public health issue.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than one billion prescriptions every year. Generics represent greater than 80% of all prescriptions dispensed in the U.S., but only 27% of expenditures on prescription drugs. GPhA is the sole association representing America's generic pharmaceutical sector in the U.S.

GPhA has reviewed the questions identified in the above referenced Federal Register Notice. Please note that GPhA is providing comment for only those questions for which our member companies have specific questions and recommendations.

A. General

Q3(ii): When do intermediate stability studies need to be initiated in the event of failure at accelerated condition?

- If a firm learns from development studies that the product cannot withstand accelerated stability condition, but is meets all quality attributes at intermediate stability conditions, then is it acceptable to keep only exhibit batches on intermediate stability and CRT condition (and not on accelerated stability)?

Q3 (iii): If one among the three batches in accelerated conditions show a significant change, what should be done?

- How much intermediate data is required to support 24 months expiry in the event that accelerated conditions fail?



- If significant change or failure occurs within the first 3 months at the accelerated storage condition, and testing under the intermediate storage condition is initiated, the requirement to continue testing of the accelerated samples through 6 months should be removed. In this case, the available stability data under the accelerated condition (i.e. 3 months), 6 months of stability data under the intermediate storage condition, and 6 months of stability data under the long-term storage condition should be acceptable at the time of ANDA filing.

Q4: Can stability bracketing and/or matrixing be used to determine the configurations to be placed on stability for an original ANDA without prior approval from the Office of Generic Drugs (OGD)?

- Do Bracketing and Matrixing stability protocols require prior approval by FDA? If yes, what is the mechanism to secure FDA approval (i.e. would controlled correspondence be an appropriate mechanism)?
- Can we submit bracketing/matrixing protocol as part of the post approval commitments for changes and annual stability study batches in the original ANDA submission?
- Is it acceptable to produce three lots for the highest and three lots for the lowest strengths as well as the RLD strength (if not included in the highest and lowest strengths) and only produce 1 lot of each of the additional strengths to be in support of the biowaiver requirements?

Q7: How is the proposed expiration date supposed to be calculated? Will 6 months of accelerated data equal 24 months at long-term?

- Please define what is meant by “long term data without variability”?
- GPhA has concern about undefined terms that may allow significant reviewer subjectivity as well as uncertainty of Agency expectations by industry. Please define “little variability.”

Q10: How long do the three pilot scale batches, submitted as a part of an ANDA, need to be stored before destruction?

- Please clarify if the recommendation for one year post-approval storage applies to the all ANDA submission batches or the reserve samples (i.e. a subset of the entire batch). Will the requirement of sample retention be applicable for “Tentative Approval” as well? What if the batch expires long before the final approval of the ANDA?

B. Drug Master File

Q1: Please clarify the effect of the stability guidance on Drug Master File (DMF) holders.

Q1(ii): How many months of long-term and accelerated data are required when a “Completeness Assessment” is performed on the DMF? Also, what should the DMF stability section contain for the same?

- GPhA believes that stability data for APIs should apply to active ingredient information submitted in ANDAs or DMFs. Please confirm if the same API stability requirements at the time of submission apply to API stability data filed in a DMF or an ANDA (i.e. an ANDA will be accepted for review containing API stability data at the initial time point and one additional time point for the accelerated studies and long-term studies).
- If an API DMF is filed containing stability data for the initial and one additional time point for accelerated studies and long-term studies and later amended with the complete six months stability data on all three batches, under GDUFA, there is no penalty in the review clock of the DMF or ANDA. GPhA believes that the same principles apply to API stability data filed in an ANDA, i.e. if an ANDA is initially filed containing API stability data at the initial time point and one additional time point for the accelerated studies and long-term studies and later amended to provide complete six months API stability data on all three batches, under GDUFA, there is no penalty in the review clock of the ANDA. We ask that FDA confirm this position.

C. Drug Product Manufacturing and Packaging

Q1: Can the split bulk solution filled into different fill volumes be considered different batches?

- Can you perform 3 common granulations using a minimum of 2 separate lots of API and compress the granulation into all of your strengths (i.e. One common granulation yields all three strengths and the second and third granulations are compressed as the highest and lowest strengths inclusive of RLD)?

Q5: Should the small scale batches be packaged with commercial equipment, or is it acceptable to package using research equipment or by hand?

- The same principles should apply to packaging equipment as applied to manufacturing equipment. Pilot scale packaging equipment with the same operating principle and design as the commercial equipment should be acceptable. GPhA requests that FDA revise its recommendations accordingly.
- We believe that industry should be able to utilize multiple pieces of equipment for packaging of the exhibit batches when they equate to the commercial packaging line. For example, firms should be able to utilize a filler, an induction seal machine, a torque checker, and labeler of the same design as that on the commercial line. The only difference is the quantity of bottles that can be packaged in the same amount of time. Therefore, the packaging of the small scale batch is representative of commercial operations.



Q7: What are the recommendations for stability testing of modified release products?

- Frequently, OGD requests the addition of one commercial batch size for modified release products. We request clarification concerning OGD expectations around the necessity for one of the three batches to be commercial scale.

Q10: Should the executed batch records for the three batches be included in the ANDA submission?

- Please clarify if the same three batch record requirement should be applied to API batches filed in a DMF or ANDA.

Q13: What is meant by “small” scale? “Small” is not a defined word in ICH guidance. What are the packaging expectations from the small batch, as well as from the two pilot scale batches? Traditionally, ANDAs are submitted with 100,000 units for solid oral dosage forms. Is this still applicable?

- The guidance states that a “minimum of 100,000 units in all proposed presentations is recommended.” Does this apply also to the “smaller” batch? If it does then the ability to use a “smaller” batch” becomes a moot point.
- What is the significance for 100,000 units of each strength? How was this number determined?

Oral Dosage Forms:

- Please clarify if the 10% proposed maximum size commercial batch is based on finished packed units or the bulk solution batch size.
- How many batches need to be tested for split-portions of scored tablets?

Parenterals:

- Please clarify if the 10% proposed maximum size commercial batch is based off of finished packed units or the bulk solution batch size.
- The 50 L pilot batch size was never proposed by FDA until publication of the Q&A document. FDA provides no scientific basis for such a requirement nor has it provided any data to support such a requirement. For many products, including cytotoxic materials and others, the actual commercial batch scale may be 50 L or less. Production of 50 L pilot batches when commercial scale batches are 50 L or less results in unnecessary environmental considerations especially for cytotoxic agents. GPhA respectfully requests that the Agency reconsider the 50 L batch size requirement for parenteral products UNLESS there is data to suggest that smaller scale batches may not represent commercial operations.

Transdermal Patches:

- Please clarify if the 10% proposed maximum size commercial batch is based off of finished packed units or the bulk matrix laminate.

Topicals:

- What packaging type (ie. bottles, blisters etc.) or pack size (30's bottle, 100's bottle, 10's blister etc.)?
- Please confirm that a 10% commercial scale batch size is based off of the bulk pre-filled cream/lotion/gel batch. MAPP 5225.1 indicates that semi-solid products should be fully packed or FDA will issue the ANDA a refusal-to-file. This is inconsistent with the statement that "we recommend packaging representative samples from all three batches".

Q18: Do small scale batches need to be produced at the proposed commercial site?

- GPhA requests that FDA revise the commendation that all batches must be produced at the proposed commercial site. Small scale batches are the same as batches produced for submission in a separate R and D pilot area in the same facility that mimics operations in the commercial area. Companies then do a tech transfer from the smaller scale area to the commercial area in preparation for validation and launch.

Q19: In cases where an intermediate bulk material is identical between the various strengths (dose proportional blends, bulk solutions, etc.), is it sufficient to perform stability on one lot of each strength, when each strength is produced from a separate intermediate bulk?

- When we have a multi-strength capsule product that is dose proportional across all strengths (common bead blend) but there are differences in the capsule shell (i.e. imprint/color, size, etc.), does the approach provided in A19 still apply?

Q21: Are scale-up and postapproval changes (SUPAC) level one and two variations and changes permitted among the three ANDA submission batches for components and composition?

- SUPAC level one changes are permitted during process validation and reported in the annual report, is it acceptable to have SUPAC level one changes between exhibit batches as they are unlikely to have any detectable impact on formulation quality and performance?

D. Amendments to Pending ANDA Application

Q1: What are the recommendations for amendments and responses filed to pending ANDAs after issuance of the new guidance?

- We request clarification as to whether this also applies to the submission of new strengths and new formulations that may have additional biostudy requirements and or that go through an amendment screening review after submission.
- What is meant by "...unless there is concern with the submitted stability data" in the answer?



- For amendments to include additional strengths listed by a brand to an application that was submitted after 6/20/2014, are we expected to produce 3 exhibit batches for each of those strengths, or can we just produce 1 exhibit batch?

Q3: When and how are reconstitution/dilution studies performed?

- Please confirm that the in-use studies that are performed as a one-time study would be performed on the all three batches.

E. Stability Studies

Q1: What will be the expected testing time points on accelerated conditions?

- GPhA requests that FDA eliminate the requirement for a fourth time point. FDA has stated in its draft guidance and final guidance that the purpose for the changes to ANDA stability testing is to be consistent with ICH. ICH does NOT include a fourth stability time point for accelerated testing conditions. No other highly regulated region of the world requires the fourth stability time point. GPhA met with FDA to discuss changes to the stability requirements over the past three years (check dates). FDA never proposed a fourth time point. In fact, such a requirement was never actively discussed in these meetings. This requirement appears in the final guidance without any scientific justification or support for the requirement and is inconsistent with the Agency's rationale for changing ANDA stability requirements, that is, to conform to ICH. Until such time that a fourth time point can be discussed with the generic industry and scientifically justified, GPhA requests that this requirement be deleted from the guidance.

Finally, we believe the FDA is the only regulatory body qualified to make the public health decisions regarding stability testing, and we support FDA's efforts to work towards the development of a clear and proven Guidance.

Sincerely,

A handwritten signature in black ink, appearing to read "D.R. Gaugh". The signature is fluid and cursive, with a large initial "D" and "R".

David R. Gaugh, R.Ph.
Senior Vice President for Sciences and Regulatory Affairs