GPhA CMC 2014 Texting Questions

Please Note: additional entries will be made to this posting as GPhA finds additional clarity. If you have additional concerns or questions please contact the appropriate FDA staff and your company's counsel. Additional DMF questions can be answered by visiting http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046.

Challenges Complying with the Stability Guidance

1) **With regards to liquids and semisolids how much of each of the three batches must be packaged? The packaging recommendations are as follows:**
    a. Powders/solution/suspension: at least 10% of the proposed commercial scale but not less than 25% of the pilot scale.
    b. Parenterals: at least 10% of the proposed commercial scale or 30 L (if fill volume is 2.0 mL or less) or 50 L (if fill volume is > 2.0 mL), whichever is larger.

2) **Do all batches need to be completely packaged or is partial packaging acceptable?** A minimum of 100,000 units packaged from ***all three batches*** is recommended. Further, all manufactured product should be packaged. If bulk packaging is used, the bulk package label with container closure information and stability data should be submitted.

3) **The May 2014 Q&A question 13 that talks about packaging expectations. Under what category of dosage form would an oral film apply? Would it fall under a transdermal patch or oral dosage form (tablets/capsules)?** An oral film product is classified as an oral dosage form. It will need to meet the minimum packaging requirements of 100,000 units to be packaged from all three batches as stated in Q13 of the Q&A guidance, Oral Dosage Form (a).

4) **Are 3 batches with 6 m stability needed for alternate manufacturing sites, drug product manufacturing scale ups, drug substance manufacturing process changes etc. or does the response pertain to only additional strength amendments ? What are the batch requirements for filing an additional strength as a PAS?** FDA new stability guidance requirements apply to all new ANDAs, Type II DMFs that supports an ANDA and new strength amendments and supplements received on or after June 20, 2014.

5) **Can FDA speak to whether parenteral products in glass would be required to be stored on stability in full packaging as labels, cartons and inserts would not be expected to have product impact? Or what packaging components would be required?** Please refer to: ICH Q1A(R2) section II, B, 4, Drug Product Container Closure System.

6) **In relation to the Guidance for Industry ANDA Stability Testing Q&A Section E Q2: Does the requirement for inverted (or horizontal) and upright (or vertical) orientations apply to syringes?** Yes. For pre-filled syringes orientation should be upright and horizontal.

7) **For an injectable dosage form having 2 to 8C as labeled as well as long term storage condition, if a significant change is observed at 25C which is an accelerated condition, how can a firm file an ANDA as there is no intermediate condition in this case?** If 6

month accelerated data fails/significant change occurs, the ANDA will need 6 months of intermediate data on the batches at the time of filing. It is recommended accelerated, intermediate and long term stability studies be started at the same time so the data is available at the time of submission in the event the accelerated study fails or there is significant change. Additionally, the submission should contain a failure analysis to provide understanding and clarity of the failure.

8) **Can you clarify the split fill/discrete batch statement? For sterile injectable solutions, to satisfy the 3 batch requirement, can we make 3 discrete bulk at 50 L each and split fill 3 strengths (2, 5, 10 mL) for each bulk? We would have 3 fills for each strength from 3 bulk. Also, for SOD, total is 100,000 for 3 batches for common blend, but for parenterals, each bulk has to be 50L and not 50L total of 3 batches, correct?**

   Injectable: 50 L size batch (discrete/separate) will be considered one batch, and three discrete batches are recommended. Split filling from each of these batches into different fill volumes will be acceptable.

   SOD 100,000 units packaged from three batches to meet filing requirement and to run stability studies; however, the firm should meet the pilot scale defined in the ICH Q1A (R2). Pilot scale is 10% of commercial or 100,000 units whichever is greater.

   SOD and parenteral products are to be treated differently.

   Please refer to: Guidance for Industry: ANDA Stability Guidance.

9) **If you are an injectable site that does not split fill, and have multiple strengths (5, 10, 15, 20, 30ml) do we need to submit 3 batches for each vial (15 batches) or can we submit 3 of the low fill, 3 of the high and 1 of the middle? Would this be acceptable?** Three discrete batches are needed. One of the batches can be used to fill all strengths. The other two batches can be used to fill the highest and lowest strengths.

10) **For injectable is secondary packaging required for all three batches?** The recommendation for secondary packaging is outline in: ICH Q1A(R2) section II, B, 4, Drug Product Container Closure System.

11) **For pre-filled syringes, can the vials only be put on stability or do you have to put it in the pen/injection device then put it on stability? If yes, what would be the upright orientation then?** The syringe and plunger will be sufficient to place on stability for pre-filled syringes. The orientation should be upright and horizontal.

12) **If there are three strengths of tablets, is it required to meet the 100,000 requirement for packaging of each strength? Or split between the highest and lowest strength?** The minimum requirement of 100,000 units packaged for oral solid dosage form should be a representation of all proposed strengths for that ANDA submission at the time of filing.

13) **Dr. Atwal's presentation mentioned the requirement for 3 batches with 1 API lot and a fourth batch with the second API lot. Does this mean 4 submission batches are required for submission or should the 3 be 2 for a total of 3 submission batches?** Dr Atwal’s presentation slide indicated that for a single source API, 3 submissions batches are

required. If the API is from two sources, than 3 submission batches are required from source A with an additional one submission batch from source B.

14) **Batch size for non-sterile topical solutions is not defined in the guidance, only sterile is listed. What is the batch size for non-sterile topical solutions?** Please refer to: Q&A guidance Q13, A13, Topicals(a), page 10.

15) **Powder for injection i.e. aseptic ally filled dry powder - what batch size should be considered for dry powder for injection where in the sterile API and or sterile blend of is aseptically filled into vials as this is not specified in Q&A?** The minimum packaging requirement for parenteral products is 10% of the proposed commercial scale. Additional packaging requirements can be found in 21 CFR 211.166(a)(1-5) and 211.166 (b).

16) **What is the batch size requirement for sterile inhalation solution packaged in blow fill seals?** Please refer to the following guidance's for industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation, and Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

17) **DMF stability - is one batch sufficient?** No. The new stability guidance requirements will apply.

18) **Q1: As per section II.C.A.20, for drug products using controlled drug substance that need DEA allocation, pilot batches can be smaller. What would be the smallest batch size acceptable?** According to the ICH definition, a ANDA batch can be smaller in size when any of the following circumstances prevails:
    a. The RLD has an orphan designation.
    b. Use of a controlled drug substance is based on a DEA allocation.
    c. The test batch size is the same as the commercial batch size with the commitment that a PAS will be provided when there is a scale-up.

    The ANDA applicant should provide a detailed justification within the ANDA submission as to the reason(s) its batch size is smaller for review and consideration during the technical review.

19) **Will the agency refuse the ANDA filing if there's no stability data for placebo tablets?** One batch of placebo tablets with full CMC information should be included at the time of the ANDA submission. The final packaging presentation (drug product with placebo for all proposed strengths) should have 6 months of accelerated and long-term stability data.

20) **If the stability in the original application supports a 36 month expiry dating, what stability info is required for the same expiry dating for post approval change?** No additional stability data would be required to support a 36 month expiry dating post approval.

21) **The GDUFA Guidance for Industry Q&A indicates that API and FDF sites may withdraw their consent to be named in an ANDA application. If they notify FDA that they have withdrawn consent they will no longer be considered to be identified in the application. If the only API/FDF site listed for a function withdraws their consent to be named in the application, what is the effect on the ANDA? Can an ANDA exist with no**

site capable of performing a given function? No. All ANDAs, pending approval or already approved and are not withdrawn from market, will need to have an API and FDF site listed in support of that application. The Agency will notify the applicant/owner of the ANDA that an API or FDF manufacturer is requesting a withdraw from the ANDA (if that notification is received directly from the manufacturer). It would be the responsibility of the applicant/owner to submit a correspondence indicating the site that will replace the withdrawn site. Please refer to: Guidance for Industry, Generic Drugs User Fee Amendments of 2012 Q&A Revision 1, September 2013, Q38.

22) **In relation to the Guidance for Industry ANDA Stability Testing Q&A Section B Q3: is one representative batch of API sufficient in the case where there is no DMF and the drug substance information is provided as a 3.2.S section.** This section refers to batch records. One representative executed batch record will suffice for all three batches.

23) **I just wanted to confirm that extractable/leachable and preservative testing is only required on one primary batch for OGD. Recently we have been asked for data on all 3 batches for several NDAs.** One of the primary batches of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the end of the proposed shelf life. The drug product specification should include a test for preservative content. This attribute should be tested in all stability studies. In general, extraction and leachable studies is performed once but if multiple types of containers/closures are proposed for packaging, then additional studies could be recommended.

24) **If an ANDA is submitted prior to the stability guidance and is subsequently amended after the stability guidance implementation to add additional strengths will it be grandfathered into the 1 batch, 3 month stability requirements?** No. All subsequent new strength amendment(s) received on or after June 20, 2014 ***will be required*** to meet the new stability recommendation of 3 batches/6 months.

25) **For split tablets stability, FDA requires 90 days stability in pharmacist dispense bottles, does FDA means small orange plastic bottles? Or the HDPE bottles? The orange bottles might not be compatible with the DP & they are not meant to withstand 90 day ICH condition.** Stability testing should be performed in the proposed container/closure presentation which supports the ANDA submission.

26) **My question is related to split tablet testing of scored tablets of not divided dosage. It is very difficult to break the tablet exactly half and maintain the fragments of half tablet and test quantitatively. What is suggestion by the agency?** Please refer to: Guidance for Industry, Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation.

27) **When using a bracketing approach to a 3 strength product, 3 batches of the highest and lowest strengths would be manufactured and placed on stability. There is no expectation to manufacture batches of the middle strength for the ANDA, correct?** All 3 strengths should be manufactured and stability testing should be completed on the highest and lowest strength for all time points as in full design. A bracketing design assumes that the stability of the intermediate levels is represented by the stability of the extremes tested. Please refer to the ICH guidance for industry on Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.

28) **If the Initial ANDA is filed with 6 months of Intermediate data (30/65) in the event of failure at accelerated, what should be the proposed shelf life for an ANDA holder at the time of submission?** FDA will grant a shelf life period of 2 times the available long-term data at the time of approval, up to 24 months, provided that the submitted data is satisfactory, and data evaluation and appropriate commitments are provided in accordance with ICH Q1E. The ANDA should be updated with 12 month of long-term data during the review cycle. Please refer to: ICH Q1E guidance, Evaluation of Stability Data.

29) **If accelerated stability data fails for a solid oral drug does the intermediate stability data need to include all ICH testing time points through 6 months? For example can samples be stored at intermediate conditions and testing initiated at 6 months if needed as backup to accelerated data that fails at 6 months.** If accelerated data show a significant change or failure of any attribute in one or more batches, intermediate data for all 3 batches should be submitted. Additionally, the submission should contain a failure analysis to provide understanding and clarity to the cause of the failure. Further, accelerated, intermediate and long-term stability studies should be started at the same time so the data is available at the time of submission in the event the accelerated stability study fails. ICH Q1A testing frequencies are:
    a. Accelerated: 0, 1, and 6 months (ICH Q1A(R2) recommendation applies for the 4^{th} time point)
    b. Intermediate: 0, 6, 9, and 12 months if accelerated data shows failure or significant change
    c. Long-term: 0, 3, 6, 9, 12, 18, 24, 36 months

30) **To pass a DMF completeness assessment, RT & accelerated stability data points of t=0 and one additional point is required. Is a t=1 month additional point acceptable or must this be a t=3 month point per ICH guidelines?** Yes. A t=1 month would be acceptable for a DMF completeness assessment.

31) **When a company is using 2 API suppliers, would 2 lots of finished product manufactured from each source be acceptable for a file able ANDA?** Yes. A minimum of 2 lots of the API should be used to prepare the 3 primary batches of the drug product.

32) **Any ANDA filed before June 20th gets RTR for any reasons, will it be agency's expectation to comply with new stability guidance at the time of responding RTR? I.e 3 batches and 6 months stability?** Yes. All ANDAs (originals, new strength amendments/supplements and or response to RTR) received on or after June 20 will be required to comply with the new stability requirements.

33) **Please provide more clarity for the calculation of 6 months for ACC testing. Does 6 months mean 180 days? Calendar days or business days?** The conversion from months into days should be calculated in terms of calendar days.

34) **In regards to the current 356h form, is the establishment info required to be listed for original applications only or for all types of submissions?** The Form 356h is required for all types of submissions.

35) **How many batches for each tube sizes are required for semi solids (gel) submission?** For nonsterile semi-solids dosage forms, the 2 pilot scale batches should be at least 100 Kg or 10% of the production batch, whichever is larger, packaged. The 3rd batch can be smaller than 10% of the proposed commercial batch but not less than 40% of the pilot scale batch, packaged. Please refer to 21 CFR 211.116 (a)(1-5) and 211.116 (b).

36) **For nasal, is FDA anticipating inverted orientation even though we submit upright and sideways orientations?** For primary batches of liquids, solutions, semi-solids, and suspensions the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position. The worst case orientation should be adapted for the study.

37) **For comparative dissolution testing of an IR or CR tablets/capsules, are we required to test one or all three primary batches?** Comparative dissolution data from 3 batches should be used to set dissolution specifications. Please refer to: Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Adminsitered Drug Products – General Considerations.

38) **What is expected to be tested on placebo tablets?** One batch of placebo tablets with full CMC information should be included at the time of submission. Also the final package presentation which contains the placebo should have 6 months of accelerated and long-term stability data to support the submission.

39) **Should intermediate samples be tested without knowing 6 month accelerated sample is going to have a significant change?** It is recommended that testing be performed on intermediate samples in the event of significant changes to the accelerated study. An accelerated, intermediate and long-term stability studies should be started at the same time so the data is available at the time of submission in the event the accelerated stability study fails or indicates significant change.

40) **If two API suppliers are to be used, can you make only 3 drug product lots for stability?** In the instance were 2 API suppliers are used, it is recommended that 3 submission batches are produced by one source and 1 batch is produced by the second source for a total of 4 batches.

41) **Per section II.C.A.20, for drug products using controlled drug substance that need DEA allocation, pilot batches can be smaller. What would be the smallest batch size acceptable?** According to the ICH definition, a ANDA batch can be smaller in size when any of the following circumstances prevails:
    a. The RLD has an orphan designation.
    b. Use of a controlled drug substance is based on a DEA allocation.
    c. The test batch size is the same as the commercial batch size with the commitment that a PAS will be provided when there is a scale-up.

    The ANDA applicant should provide a detailed justification within the ANDA submission as to the reason(s) its batch size is smaller for review and consideration during the technical review.

42) **If we have one batch of DP with 3 month Acc data and 24 month CRT data, and 2 batches with 6 M Acc and 6 M CRT data, will agency accept the filing?** As outline in

the new stability guidance, 6 months accelerated and 6 months long-term data on 3 batches should be provided at time of submission.

43) **If the product is going to be submitted in aluminum foil and child resistant blisters. Do we need to submit both or can we use the aluminum foil as a worst case and do not submit child resistant package stabilities?** Stability testing should be performed on all proposed packaging presentation(s).

44) **It is clarified that 12 month of LT will give 24 month shelf life but at the time of submission we have 6 months. Can we state proposed shelf life of 2 years in the ANDA?** Yes. FDA will grant a shelf life up to 2 years (2 times the available long-term data at the time of approval) provided that the submitted data is satisfactory and the data evaluation and appropriate commitments are provided in accordance with ICH Q1E. The ANDA should be updated with 12 months of long-term data during the review cycle.

45) **As per IID amount per unit is imp But RTR hints on MID which is important?** For the purpose of filing the submission, for solid oral dosage forms, the IID justification should be based on the per unit dose amount of each excipient. For liquid oral products the justification should be based on the actual dosage of the product and not based on the concentration of the excipient within the drug product. The MDD (maximum daily dose) or the MDI (maximum daily intake) should be provided for each excipient used in the drug product formulation to facilitate the filing review process. Please refer to: Guidance for Industry, ANDA Submission – Refuse to Receive Standards.

46) **How are sublingual film oral tablets categorized? Oral tablet or transdermal film?** Sublingual film products are categorized as a solid oral dosage form, sublingual or buccal.

47) **What type of recommendation do you suggest for evaluation of stability data in case of stability failures at accelerated stability condition for shelf life considerations?** FDA will grant a shelf life period of 2 times the available long-term data at the time of approval, up to 24 months, provided that the submitted data is satisfactory, and data evaluation and appropriate commitments are provided in accordance with ICH Q1E. The ANDA should be updated with 12 month of long-term data during the review cycle. Please refer to: ICH Q1E guidance, Evaluation of Stability Data.

48) **Is an Annexure Index of CMC Information required in Annual Reports?** Please refer to: Guidance for Industry – CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports.

49) **With supplement, do we need to do 3 months accelerated study for submission or 6 months?** The guidelines from the new stability guidance would apply.

50) **For CBE-30 supplements, is the FDA assessing the supplement filing category within the 30 day window such that industry would be notified if the supplement needed to be upgraded to a PAS by day 30?** The Agency is currently assessing the submitted supplement filing category of CBEs and PAS. In the event a submitted CBE needs to be converted to a PAS, the Agency will notify the applicant via a letter. The Agency is making every effort to assess these submission types in a timely manner.

51) **Is it required to perform dose dumping dissolution studies for all batches of all strengths?** Comparative dissolution testing should be performed on twelve individual dosage units of each proposed strength (from each lot) to the reference product. Due to dose dumping concerns of certain drug products, additional dissolution testing may be required. In these instances, it is recommended that both the proposed and reference products be tested and data provided with regards to the testing parameters as outlined in the Bioequivalence Recommendations for Specific Products Database for all strengths of the proposed and reference.