



Regulatory Education for Industry (REdI): **GENERIC DRUGS FORUM**

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ANDA Stability Guidance(s)

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Agenda

- **ANDA Stability guidance and Q&A Guidance**
- **Q1D – Bracketing and Matrixing**
 - **Bracketing (strengths, & containers)**
 - **Matrixing while considering an ANDA**
- **Packaging**
- **Q1 E**
- **Other items**



Highlights – ANDA Stability Guidance

1. Submit data from three pilot scale batches **or** two pilot scale batches and one small scale batch. If the size of the pilot scale batch does not follow ICH recommendations, the applicant should provide a justification.
2. At the time of submission, provide 6 months of data that include accelerated and long-term conditions. FDA recommends following ICH guidelines with respect to utilization of intermediate conditions to support shelf-life.
3. Use multiple lots of drug substance as appropriate.
4. Manufacture and package the drug product using principles that are representative of the commercial process.
5. Provide a fully packaged primary batch.
6. Use drug product from all three primary batches when using bracketing and matrixing designs under ICH Q1D.
7. Provide statistical analysis of the data as appropriate, in accordance with ICH Q1E, Appendix A.



Highlights – ANDA Stability Guidance

2. At the time of submission, provide 6 months of data that include accelerated and long-term conditions. FDA recommends following ICH guidelines with respect to utilization of intermediate conditions to support shelf-life.
5. Provide a fully packaged primary batch.
6. Use drug product from all three primary batches when using bracketing and matrixing designs under ICH Q1D.



Highlights – Q&A Guidance

- **Companion guidance**
 - Small scale batch size defined
 - Listed exemptions for pilot scale batch size
 - Clarified multiple lots to 2 discrete lots of API for most dosage forms
 - Miscellaneous questions



ICH Q1 D Bracketing

- **Design of a stability schedule**
 - Examples from the Q1 D guidance are strength, container size and or fill volume
 - Reference made to Q & A Guidance Section C, Q 19 (May 2014) – example for bracketing intermediate strengths
 - Extremes to be tested at all time points



Q1 D - continued

Q19(i): 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?

A19(i): No. For ANDAs that contain multiple strengths (that are dose proportional), three separate intermediate bulk granulations (or blends) should be manufactured. One batch of bulk granulation (or blend) should be used to manufacture all the strengths proposed. The other two bulk granulations (or blends) can be used to manufacture only the lowest and the highest strengths, in addition to the strength used in BE studies (i.e., the strength(s) tested in the BE studies should have three batches). Stability testing should still use all three batches of drug product.



Q1 D- continued

- **Common granulation approach where possible can:**
 - Be used to manufacture multiple strengths of a dose proportional dosage form
 - Justifies a bracketing approach for multiple strengths, and eliminates some variables during processing
 - Provides continuity.



Q1 D- continued

- **Q1 D interpretation applies to bracketing strengths when**
 - Capsules of different strengths with different fill plug sizes from the same powder blend
 - Tablets of different strengths manufactured by compressing varying amounts of the same granulation
 - Oral solutions of different strengths with formulations that differ only in minor excipients (color/flavor)



Example of multiple strengths from common granulation (Q&A 19) from the guidance

- Example presented – dose proportional strengths

Strength in mg	2	4	8	10	12
Batch #1	x	x	x	x	x
Batch #2	x	None	None	None	x
Batch #3	x	None	None	None	x



Q1 D- continued

- **When common blend is not feasible**
 - each strength needs to stand on its own (3 batches per strength)
 - matrixing may be an option to consider here



Q1 D - Matrix design

- **Reduction in testing via Matrixing is applicable**
 - **When 3 batches of each strength is made**
 - **For long-term testing stability protocol**
 - **While matrixing time points:**
 - Initial, 3 months and 6 months at long-term conditions are ANDA filing requirements
 - 12, 24 months are anniversary points and we recommend testing to facilitate approval
 - Testing to include all test attributes



Q1 D - Continued

- **Bracketing of HDPE/other containers**
 - Proportionality of configuration
 - Awareness of RLD market sizes, MDD, along with duration of therapy while planning count sizes
 - Liquids- have to have proportional container/closure attributes for determining extremes



Packaging

- **Stability guidance recommends one primary batch to be fully packaged**
 - Applies common granulation/blend is used or not
 - Use of bulk (for solid dosage forms) containers, HDPE, blisters for solid dosage forms
- **Partial packaging from the other two primary batches is acceptable**



Small scale and Packaging

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?

- **OGD filing requirement of 100,000 units from 3 batches is acceptable when a small scale batch of (the three submission batch) is made and completely packaged**
- **If ANDA comes in with three commercial scale batches then one of three batches should be completely packaged**



Other findings

- **Commercial scales batches (as primary submission batches)**
 - Still needs to package one batch completely
 - Process validation has begun – not completed (2011 FDA guidance: *Process Validation: General Principles and Practices*)
 - PAS needed for scale up



Q1E

- **Data plot and written summary is expected**
 - Assay, impurities
- **Stability commitment to test first commercial lots is expected when**
 - Small scale/pilot scale is proposed followed by larger scale
 - Satisfactory 24 months full long-term data is not present in the ANDA at the time of approval
- **Intermediate condition stability data when accelerated data experiences significant change**



CTD submission Module 3

- **ANDA stability section should contain:**
- **3.2.P.8.1 Stability Summary and Conclusions**
 - Write up of the primary batches data, analysis, proposed expiration period, differences among the packages/storage conditions etc.
- **3.2.P.8.2 Protocol and Commitments (post-approval batches)**
 - Necessary Commitments
- **3.2.P.8.3 Stability data**
 - Primary submission batches
 - Other special studies



CFR

- **21 CFR § 314.50 (e)(1)**
 - **Sample requirements apply to all three primary submission batches**
 - **Methods verification at the FDA labs**
 - **Visual evaluation during review**
 - **Consults between Center Offices**



Summary & Acknowledgement

- **ANDA stability guidance implemented on 6.20.2014; companion Q&A guidance finalized and announced in May 2014**
- **OGD/OPQ Management, Stability Work Group Members, and CMC Review Staff**

Questions?

**Please hold them till the next
presentation is done!**



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ANDA Stability Guidances Additional Considerations

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Synopsis

- **Introduction**
- **General Discussion**
- **Drug Product Manufacturing**
- **Special Topics**
- **Summary and Acknowledgements**





Introduction

- **Why Stability?**

Applicable to ALL ANDAs



Quality

Safety

Efficacy

Life Cycle of Drug Product



Introduction Contd.

- **ANDAs: Stability Testing of Drug Substance and Drug Product**
 - ✓ *Implemented on **June 20, 2014***
- **Companion Q&A Guidance**
 - ✓ *Finalized and announced on **May 2014***





General Discussion

- Applicable to All ANDAs and DMFs
- **NOT** applicable to post-approval changes
- At Submission
 - ✓ *Six month accelerated and Six month long term data on Three Primary Batches*
 - Three Pilot Scale Batches OR Two Pilot Scale Batches and One Small Scale Batch





General Discussion Contd.

- **Storage Temperature**
- **ICH recommendations are ONLY in terms of Months**
- **Application needs to be updated**
 - ✓ *Accrued Long Term Stability data*
 - ✓ *Intermediate Stability Data where applicable*





General Discussion Contd.

- **PEPFAR and PET ANDAs**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section A, Q2*
- **Qualifies for 10 month review and **NO** blocking patents or exclusivities**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section A, Q5*
- **When patent is due to expire shortly and **No** approved ANDAs**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section A, Q9*





Drug Product Manufacturing

- **A Minimum of Two lots of drug substance**
- **Two Sources of drug substance proposed**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section C, Q12*
 - ✓ *If first source withdrawn then additional data*





Drug Product Manufacturing Contd.

- **Two Sources of drug substance proposed**
 - ✓ ***Comparability of the two sources with justification***
 - ✓ ***Drug product stability data***
 - For qualification of the first source
 - To support the second source
 - Include comparative dissolution data
 - ✓ ***At the time of filing***
 - Six month accelerated and long term data
 - Intermediate data if applicable





Drug Product Manufacturing Contd.

- **Relevant information in Module 3**
 - ✓ ***More than one lot of drug substance***
 - ✓ ***More than one source of drug substance***
 - ✓ ***More than one lot of excipient/s***
 - ✓ ***Executed batch records***





Drug Product Manufacturing Contd.

- **Solid Oral Dosage Forms:
Tablets/Capsules**

- ✓ ***Two Pilot Scale batches***

- Discussion in Q&A Guidance (May 2014) under Section C, Q13

- ✓ ***Third batch smaller***

- Discussion in Q&A Guidance (May 2014) under Section C, Q13

- ✓ ***All submission batches manufactured under cGMP***





Drug Product Manufacturing Contd.

- **Solid Oral Dosage Forms:
Powders/Solutions/Suspensions**
 - ✓ ***Two Pilot Scale batches***
 - Discussion in Q&A Guidance (May 2014) under Section C, Q13
 - ✓ ***Third batch smaller***
 - Discussion in Q&A Guidance (May 2014) under Section C, Q13
 - ✓ ***All submission batches manufactured under cGMP***





Drug Product Manufacturing Contd.

- **Parenterals: Solutions/Powders for Solutions/Suspensions/ Sterile Topicals**
 - ✓ ***Two batches***
 - Discussion in Q&A Guidance (May 2014) under Section C, Q13
 - ✓ ***Third Batch***
 - Discussion in Q&A Guidance (May 2014) under Section C, Q13
 - ✓ ***All batches meet sterility requirements***





Drug Product Manufacturing Contd.

- **Criteria for exception to the recommendations regarding batch size**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section C, Q20*
- **Testing for split-portions of scored tablets**
 - ✓ *Generally, one batch for each score strength*
- **Placebo Tablets**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section C, Q24*





Special Topics

- **Expectation for storage positions**
 - ✓ ***Applicable to:***
 - Liquids, solutions, suspensions, semi-solids
 - ✓ ***Primary Batches placed on stability in:***
 - ***Both inverted (or horizontal/lateral) and vertical positions***
 - ✓ ***Routine stability on worst case orientation***





Special Topics Contd.

- **Preservative Effectiveness**

- ✓ ***One of the primary batches tested for:***

- **Anti-microbial preservative effectiveness**

and

- **Preservative content**

- **At the end of proposed expiration dating**

- ✓ **Product specification includes preservative content**





Special Topics Contd.

- **Extractable Leachable testing**
 - ✓ *Generally one time studies*
 - ✓ *Additional studies for multiple types of container/closure presentations*
- **Reconstitution/Dilution and In-Use studies**
 - ✓ *Performed when the product is so labeled*
 - ✓ *ICH recommendations are followed*





Special Topics Contd.

- **Scale up and Post-approval changes**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section C, Q21*
- **Recommendations for amendments to pending ANDAs**
 - ✓ *Discussion in Q&A Guidance (May 2014) under Section D, Q1*





Summary and Acknowledgements

- **Stability Guidance and Companion Q&A Guidance Document finalized**
- **Discussion of Stability Topics after implementation on June 20, 2014**
- **OGD/OPQ/OLDP Management**
- **Stability Working Group Members**
- **Quality Reviewers**





Questions?

Evaluation: surveymonkey.com/s/GDF-D2S5