ANDA Stability Guidance
Opportunities & Challenges

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Agenda

• Introduction
• Opportunities & Challenges
• Conclusions
Introduction

• **Guidance for Industry**
  ANDAs: Stability Testing of Drug Substances and Products

• **Guidance for Industry**
  ANDAs: Stability Testing of Drug Substances and Products
  Questions and Answers
Introduction contd.

• History of development
  – 2011, 2012, 2013 Presentations, and in-house meetings held with stake-holders and FDA including GPhA Workshops
  – Questions from the Industry and GPhA were collected for responses; draft Q&A guidance was published
Two webinars (DIA, and SBA) were hosted by the members of the stability working group
Implementation

• June 20, 2014 is the implementation date
• The Q&A guidance will assist in the adoption
• Referenced ICH Stability Guidances:
  – Q1A(R2) – Stability Testing of New Drug Substances and Products with Glossary
  – Q1B – Photo stability Testing of New Drug Substances and Products
  – Q1C – Stability Testing of New Dosage Forms
  – Q1D – Bracketing and Matrixing Designs for Stability Testing of New Drug Products
  – Q1E – Evaluation of Stability Data
Opportunities

Multiple API Sources

• A minimum of two lots of API to be used for making the primary batches

• Allowance for proposing two API sources at the time of original ANDA submission
  – 3 submission batches from one source, and one submission batch from the second source
  – See Q & A document

• DMFs are already following ICH requirements for submission purposes
Challenges

Multiple API Sources

• API Batches made under GMP are to be used for manufacturing DP batches
  – Batches made with technical grade API will be considered as supporting data, but not considered as primary batches
Opportunities and Challenges

Batch size

• Definition of **small scale batch size** for ANDAs – provides the industry some basic concept of how small a small scale can be accepted
  – Oral solids, liquids, sterile solutions, transdermal patches etc.
  – Small scale batch size is **not the same** for all dosage forms
  – Orals – at least 10% of production batch but not smaller than 25% of pilot scale (25,000 units/tablets/capsules )
  – Powder/solution/suspension: at least 10% of the proposed commercial scale, but not less than 25% of the pilot scale
  – Parenterals – at least 10% of proposed commercial scale, or 30 L (if fill volume is 2.0 mL or less), or 50 L (fill volume >2.0 mL), which ever is larger, packaged.
Opportunities and Challenges

Batch Size contd.

• Transdermal Patches – at least 10% of the proposed commercial batch packaged, but not less than 60% of the pilot scale packaged; for different strengths (identified by patch size/surface area) three distinct matrix laminates are recommended

• Topicals, non-sterile (creams, lotions, and gels) – at least 10% of the proposed commercial batch, but no less than 40% of the pilot scale packaged

• Placebo/inert tablets where needed: Only one batch to be made and submitted at the filing time; the final packaging presentation including placebo will need 6 months accelerated and long-term stability data at the time of submission
Exception to ICH batch size- Opportunity

• The submission ANDA batches can have a smaller size than the established pilot scale, according to the ICH definition, under the following circumstances:
  – The reference listed drug product has an orphan drug designation
  – Use of a controlled drug substance is based on a Drug Enforcement Administration allocation
  – The test batch size is the same as the commercial batch size with the commitment that a prior approval supplement (PAS) will be provided when there is a scale-up
Opportunities
Packaging

• Oral dosage form:
  – Minimum 100,000 units packaged from all three batches – retained the OGD’s current expectation of accepting the same amount, but it has to come from all three batches

  – Packaging expectations for other dosage forms are similarly defined in the Q&A guidance/document
Opportunities and Challenges
Dose Proportional Blends, And Bulk Solutions etc.

• Although three separate bulk granulations or blends need to be manufactured, only one batch needs to be used for all the proposed strengths; the other two can be used for the lowest and the highest strengths (in addition to the strength used in the BE studies).

• However, the stability testing should still use all three batches of drug product
Other Challenges and Opportunities

• Splitting a bulk solution batch into discrete fill volumes cannot be considered as three discrete batches
• Hand packaging is not recommended for the small scale batches
• Blow-fill-seal containers are to be treated the same way as the other products that need secondary packaging
• All three submission batches should have the same components and composition, manufacturing site, and specifications
Other Challenges and Opportunities contd.

• For Preservative effectiveness, only one of the primary batches need to be tested; preservative content should be tested in all batches.

• In general only one primary batch is to be tested for leachables/extractables. However, if multiple types of container closures are used, additional studies could be recommended.
Opportunities and Challenges
Bracketing and Matrixing

• Stability protocol may include bracketing or matrixing w/o a prior controlled correspondence being approved as ICH Q1D allows this
• Example recommendations are to be followed from Q1D guidance itself

Bracketing: No change from current policy
• Allows for testing only the samples on the extremes of certain design factors (container size/fill/strength) at all time points as in a full design
Matrixing Opportunities

**Matrixing:** Some sub-sets of samples would be tested at some time points

- Assumes stability of each subset of samples tested represents the stability of all samples at a given time point
- Recommends full testing at certain time points (e.g., 0, 12, 24, 36 months etc.)
- More suitable for long-term testing protocols than accelerated, or intermediate testing
- Recommends against matrixing across test attributes
Opportunities and Challenges

Stability Protocol and Commitments

• ICHQ1A(R2) recommendations are to be followed
• If pilot scale primary batches are submitted, then 3 production scale batches are to be placed in accelerated and long-term conditions
• If long-term data from three production batches covering the proposed shelf life is provided, then a post-approval commitment is not needed to place on stability 3 commercial scale batches
• One annual batch to be placed on stability, if manufactured, and provide stability data in AR
Stability Data Presentation Challenges

• What is different from current expectation?
• Data Analysis (per Q1E)
  – All three batches’ data to be included
  – Use of Appendix A: Decision Tree for shelf life estimation (excludes frozen DP)
  – Use of (tables), narrative, and graphs
  – Graphical format for assay, impurities/total impurities, and other critical attributes such as pH, vs. time points with upper and lower limits
  – Consideration of Significant Change from ICH Q1A(R2) section 2.2.7
Stability Data Presentation Challenges contd.

- If 6 months accelerated data fails/ significant change occurs, ANDAs will need 6 months 30°C/65%RH intermediate data on batches (at filing time); more to be amended later

- Definition of Significant Change
  - In general, it is defined as one or more of the following (as appropriate for dosage form):
Significant Change
ICH Q1A(R2) Definition

- A 5% change in assay from its initial value, or failure to meet acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet acceptance criteria for appearance, physical attributes, and functionality test (e.g. color, phase separation, resuspendability, caking, hardness, dose delivery per actuation).
- Failure to meet acceptance criterion for pH.
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.
Amendments to Pending ANDAs

- All amendments submitted to pending ANDAs after the effective date of the final stability guidance (June 20, 2014) will be held to the standards in place at the time of the original ANDA submission, unless there is a concern with the submitted stability data.
Conclusions

The ANDA Stability Guidance:

• Will enhance the quality of generic drugs by reducing stability failures
• Clarifies stability expectations for OGD
• Consistent stability expectations within FDA
• Standardizing stability expectations would benefit both industry and the FDA
Implementation Plans

• Regulatory Filing staff training conducted in April 2014
• CMC Reviewer Training underway..
• The Q & A Guidance published on May 15, 2014
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