Stability Considerations for Generic Drugs

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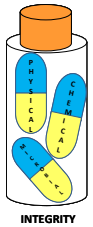
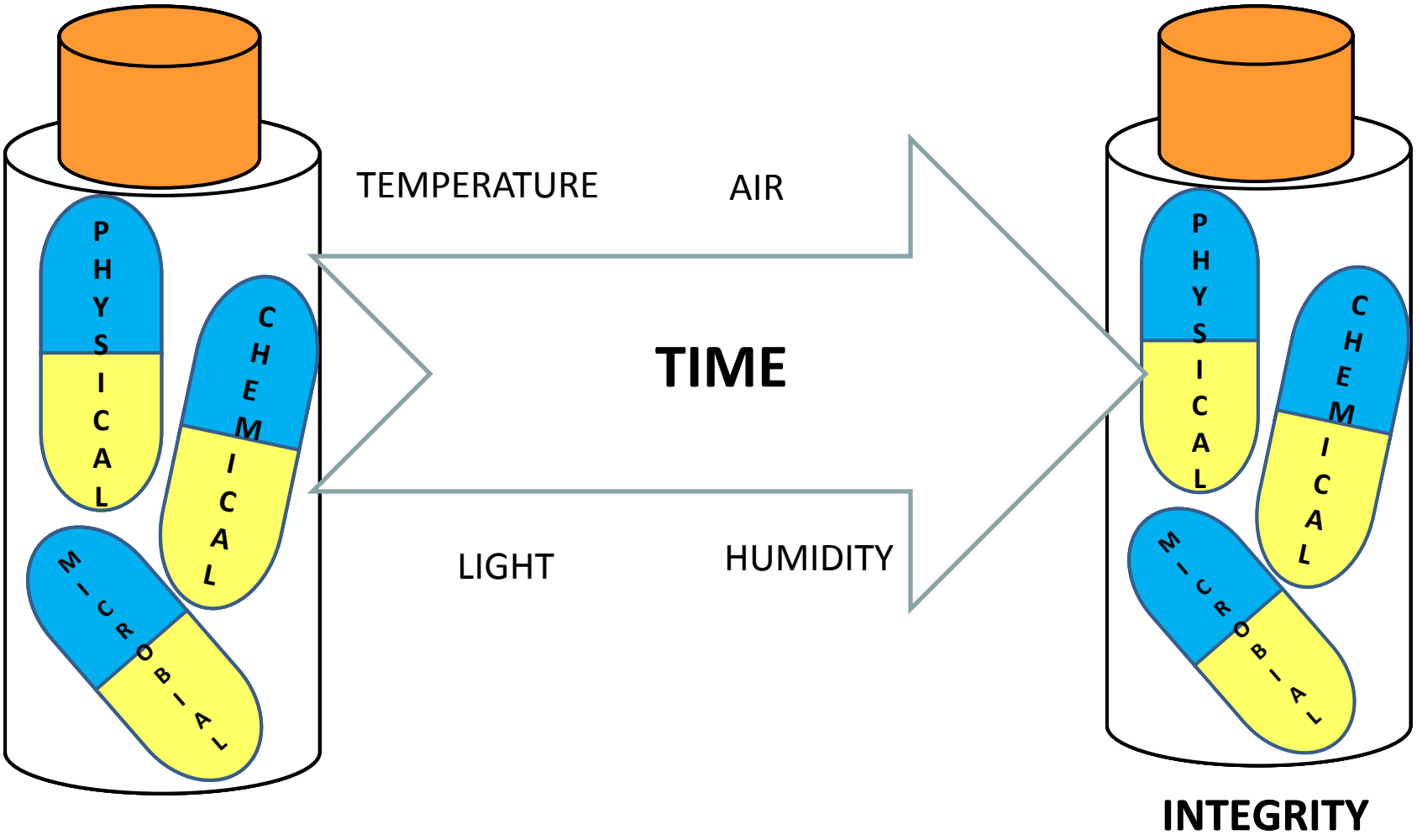
The opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or the policies of the FDA



Synopsis

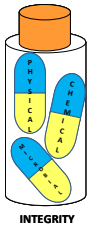
- Introduction
- Previous Communications
- Follow up on Drug Master Files (DMFs)
- Follow up on Abbreviated New Drug Applications (ANDAs)
- Summary

Introduction



Introduction Contd.

- Why Stability ?
  - *Applicable to all ANDAs*
  - *One of the indicators of quality, safety and efficacy*
  - *Managed through "Life Cycle" of the drug product*
- Therefore, a Quality Target Product Profile (QTPP)



Previous Communications

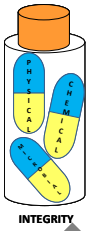
May 2011	Oct. 2011	May 2012	Nov. 2012	June 2013	Future Dates !!!
GPhA QbD Workshop	GPhA Meeting	GPhA CMC Workshop	DIA Webinar	GPhA CMC Workshop	Further Communications

Stability Considerations for Generic Drugs

Previous Communications Contd.

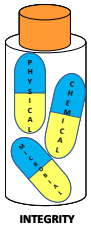
- Questions at GPhA Workshops/Meeting
- Questions to the Office
- Questions through Controls
- Questions!! Questions!! Questions!!

Follow Up is Helpful



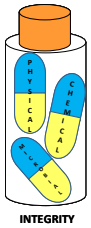
Follow Up on DMFs

- Completeness Assessment
  - *Different standard than full scientific review*
  - *Demonstration of commencement of stability*
  - *DMF is amended as additional data becomes available*
- Full Scientific Review
  - *Stability data on batches manufactured under CGMP*
  - *Batches representative of commercial manufacturing process*
  - *Stability data covering proposed retest period*



Follow Up on ANDAs

- General Discussion
- Drug Product Manufacturing
  - *Discussion of dosage forms that constitute bulk of ANDA submissions*
  - *Discussion of other dosage forms*
- Drug Product Packaging
- Stability Studies



Follow Up on ANDAs

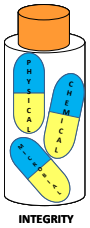
General Discussion

- Applicable to all new ANDAs and DMFs (Type II)
- **NOT** applicable to post-approval changes
- At submission Six month Accelerated and Long-term data, on Three Primary batches
  - *Three pilot scale batches or two pilot scale batches and one small scale batch*

Follow Up on ANDAs

General Discussion Contd.

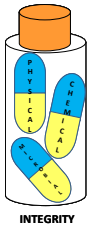
- At submission if six month accelerated data shows significant change or failure of any attribute in one or more batches, then six month of intermediate data
- ICH time recommendations are only in terms of months
- Application needs to be updated with accrued long-term stability data and where applicable Intermediate stability data



Follow Up on ANDAs

Drug Product Manufacturing

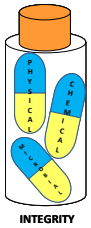
- All ANDA Submission Batches
  - *Same Drug Substance Quality intended for Market Product*
  - *Same chosen formula based on product development studies for Components and Composition*
  - *Same Specifications*
  - *Same Drug Product Quality intended for Market Product*



Follow Up on ANDAs

Drug Product Manufacturing Contd.

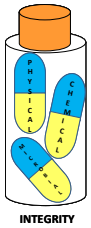
- A minimum of two lots of drug substance to be used to prepare primary batches (MDI and meter-dose spray pumps three lots)
- When two sources of drug substance are proposed
  - *Comparison and Justification by the firm of physico-chemical properties and impurities*
  - *Three batch data on one source for qualification of first source (preferably used in BE studies)*
  - *One batch (bio Strength/s) using second source(s) along with comparative dissolution data*
  - *Accelerated, long-term stability data (6 months at filing) on strengths manufactured for each source. Intermediate condition stability data could also be recommended*
  - *If first source is withdrawn additional data will be necessary*



Follow Up on ANDAs

Drug Product Manufacturing Contd.

- Module 3 should contain all the relevant information
  - *When more than one lot of drug substance is used*
  - *When more than one source of drug substance is used*
  - *When more than one lot of excipient/s are used*
  - *Executed batch records*

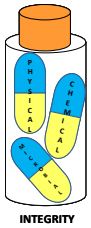


Follow Up on ANDAs

Drug Product Manufacturing

(Discussion of dosage forms that constitute bulk of ANDA submissions)

- Solid Oral Dosage Forms: Current Thinking
  - *Two Pilot Scale batches of 100,000 units or at least 10% of proposed production whichever is greater*
  - *Third batch can be smaller than 10% of proposed production but NLT 25% of the pilot scale*
  - *All submission batches manufactured under CGMP with same formulation, same specifications, and at the commercial site*

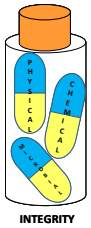


Follow Up on ANDAs

Drug Product Manufacturing

(Discussion of dosage forms that constitute bulk of ANDA submissions) Contd.

- Parenterals: Current Thinking
  - *Two batches at least 10% of proposed commercial size (i.e. pilot scale size) or 50 L whichever is larger*
  - *Third batch can be smaller than 10% of proposed production but NLT 25% of the pilot scale*
  - *All submission batches manufactured under CGMP with same formulation, same specifications, and at the commercial site*
  - *Split filling of bulk solution does not constitute discrete batches*

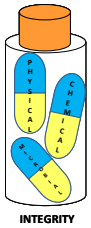


Follow Up on ANDAs

Drug Product Manufacturing

(Discussion of other dosage forms)

- President's Emergency Plan for AIDS Relief (PEPFAR) ANDAs
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf*
- Positron Emission Tomography (PET) ANDAs
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf*

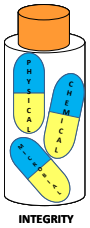


Follow Up on ANDAs

Drug Product Manufacturing

(Discussion of other dosage forms) Contd.

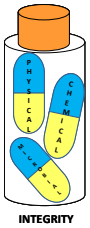
- Inhalation Solution/Nasal Spray (non-metered dose) ANDAs
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf*
- Transdermal and Related ANDAs
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf*



Follow Up on ANDAs

Packaging

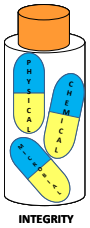
- Representative samples from all three batches must be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).
  - *Current Thinking: For Tablets and Capsules a minimum of 100,000 units in all proposed presentations is recommended.*
- Secondary Packaging as per ICH Q1A(R2) Container Closure Section (2.2.4)
- Packaging System the same as or similar to proposed for storage and distribution
- Variability introduced by packaging should be captured



Follow Up on ANDAs

Stability Studies

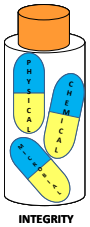
- Expectation for Storage Positions
  - *Applicable to liquids, solutions, suspensions, semi-solids etc.*
  - *Primary batches placed on stability in both inverted (or horizontal/lateral) and vertical positions*
  - *Routine stability on worst case orientation*
- Preservative Effectiveness
  - *One of the primary batches tested for anti-microbial preservative effectiveness **and** preservative content at the end of proposed expiration dating*
  - *Product specification includes preservative content*



Follow Up on ANDAs

Stability Studies Contd.

- Extractable Leachable testing
  - *Generally one time studies*
  - *When product packaged in multiple types of container/closures additional studies recommended*
- Reconstitution/Dilution and In-Use Stability studies
  - *Studies performed when the product is so labeled*
  - *Follow the ICH recommendations*



Summary

- Office of Generic Drugs (OGD) has communicated with the industry on emerging stability expectations
- Follow up on DMFs
- Covered general discussion, stability studies, drug product manufacturing and drug product packaging for ANDAs

Acknowledgements

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