Quality Considerations for First Generic Oral Liquids

Advancing Generic Drug Development 2024: Translating Science to Approval

Day 2, Session 5a:
Spotlight Generic Drug Review Challenges and Solutions

Maria Flynn, PhD

Senior Pharmaceutical Quality Assessor
Application Technical Lead
Division VIII, OPQA II
CDER | US FDA

September 25, 2024

Learning Objectives

- Assess Critical Quality Attributes (CQA) Risks for Oral Solution/Suspensions
- Describe 1st Generic Oral Liquid Case Studies Mitigating Risks
  - Understand Physical Stability
  - Confirm Chemical Stability
  - Manage Unexpected Leachable
  - Mitigate Container Closure System Risks

Critical Attributes for Oral Solution or Suspension

- **Physical Stability**
- **Chemical Stability**
- Assay
- Content Uniformity
- **Container Closure System**
- Dosing Accuracy
- Microbial Limits
- Preservative Content
- **Leachable**
- Dissolution (Oral Suspensions Only)

Physical Stability for Oral Solution or Suspension

- Solid State
- Sedimentation*
- Particle size growth*

*Oral Suspensions only

Physical Stability for Oral Solution or Suspension

- Solid State
  - Exhibits Polymorphism (>Risk)
    - Crystalline or Amorphous
    - Suspensions have >risk than Solution
  - Consider Solution Equilibria

Physical Stability for Oral Solution or Suspension

- Solid State
  - Oral Solution
    - <risk: Dissolved solution concentration is <solution equilibria
  - Oral Suspension
    - <risk: No polymorphism, or, most stable formed used, or, only amorphous form exists, and/or, highly soluble per BCS classification
    - >risk: Unstable crystalline and known solid state conversions

Case Study #1:Physical Stability for Oral Suspension

- Exhibits Solid State Risk
  - Known Crystalline Polymorphs
  - Suspensions have >risk
  - BCS class II drug (low-solubility, high-permeability)

Case Study #1:Physical Stability for Oral Suspension

Mitigate Solid State Risks

- Polymorphic Identification of Form by XRD in Drug Product Release and Stability specification
- 3-Tier Particle Size (<22 microns)
- Polymorphic Stability at 6-month Accelerated and 24-month long term

Chemical Stability for Oral Solution or Suspension

- <Risk: No trend
- >Risk:
  - Significant trending
  - Formulated with stabilization agent

Case Study #2: Chemical Stability API Degrading

Suspension's Label: Shake before Using. Store at refrigerated 2°C to 8°C/36°F to 46°F. **Avoid** freezing and **excessive heat.** Protect from light.

Stability Conditions	Results
ACC: 25 °C ±2 °C and 60% RH ± 5% RH	Significant trends in assay and out of specification (OOS) for impurities
Long Term: Refrigerated 2°C to 8°C/36°F to 46°F	Complies with criteria at **24 months** per ICH Q1E*

*Request to shorten shelf-life denied per ICH Q1E

Challenge Question #1

What is NOT an Active Pharmaceutical Ingredient (API)-related risk factor in Oral Liquids?

A. Exhibits Polymorphism

B. Dosing cup inaccuracy

C. Poor Solubility

D. Easily Oxidized (Air sensitivity)

Case Study #3: OOS* Degradant

- Failed stability data at 6-month Accelerated Stability and 24-months long term
- Exceeded the unspecified impurity limits (>ICH Q3B Identification threshold criteria)

*Out Of Specification

Case Study #3: OOS Degradant CAPA

- Investigated OOS Unidentified Impurity
- Identified, Characterized, and confirmed by synthesizing compound

Case Study #3: Identifying Degradant

- The unspecified degradant was found to be the diastereomer of the known oxidative degradant of the active (one chiral center was racemized)

Case Study #3: Understanding OOS

- What happened?
  - Preparation of 1N HCl Concentrated in a stainless steel (SS) vessel
  - Exposure time for HCl with the vessel > for batch with OOS degradant
  - HCl leached elemental iron form the SS vessel
  - Iron-catalyzed oxidative reaction of the active forming degradant during the Drug product pH adjustment
  - Degradant exceeded the unspecified limit at 6-month (OOS) during the accelerated stability study

Case Study #3: Control Strategy

- Revised DP stability specification to specify the newly observed degradant
- Controlled at the ICH Q3B Qualification threshold
- Commits to controlling this degradant in commercial batches at the lower limit

Case Study #3: Managing the Unexpected

- Submitted a well-written CAPA report
- Understood the degradant's origin to control
- Confirmed degradant's identity with synthesized compound
- Provided analytical method validation for specified degradant
- Committed and Specified degradant

Challenge Question #2

All are common deficiencies for oral solution/suspension, except for:

A. Providing a well-written CAPA report with a control strategy for unexpected findings

B. Incomplete understanding of manufacturing process

C. Not having all the stability data needed per ICH Q1E

D. Not specifying a container closer system (CCS) description and CCS integrity

Demonstrate a Suitable Container Closure System

- Describe and specify container closure system (CCS) integrity on release and stability
- Monitor and evaluate CCS configurations

Case Study #4: Withdraw Unit Dose Cups-Unsuitable Lidding

Summary

- Identified critical quality attributes and various risks for oral solutions/ suspension
- Discussed risks and mitigation with 4 case studies

Closing Thought

Know your Drug Product Risks

Mitigate Risks

Expect and investigate the unexpected

Provide clear control strategies