Analytical Considerations For Pediatric Drugs Administered with Dosing Vehicle

Pediatric Workshop

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Outline

- Challenges associated with administration using dosing vehicles
- Designing compatibility studies
- Case studies
- Questions for discussion

Special Needs for Pediatric Dosage Forms

- Need to further manipulate commercially available product before administration
  - Unable to swallow intact product (children, adolescents, elderly)
  - Palatability/taste/texture
  - Unavailability of appropriate dosage strengths to meet child's need
- May need small amounts of liquid/soft foods as a suitable dosing vehicle

Dosage Administration Considerations

- Selection of nature and amount of dosing vehicle
- Stability of the API in dosing vehicle
  - Chemical compatibility with the dosing vehicle
  - Performance of the drug product
- Ability to deliver desired dose to the patient (dose flexibility)
- Acceptability of the modified preparation
- Uniformity of drug in the dosing vehicle
- Bioavailability impact (complexation with vehicle components)
- Any safety challenge associated with modification

Analytical Method Considerations

- Analytical Method
  - Does the drug substance get exposed to vehicle?
    - If no, changes in potency or performance not expected, need to be demonstrated
    - If yes, testing for potency and performance needed
- Methods need to be validated
  - Any source of interference from vehicle should be understood and addresses
- Drug extraction/Sample handling
  - Does the drug substance dissolve in vehicle?
- Leveraging existing analytical methods

In-use Compatibility Studies

- Conducted to support the drug product use by the patient/care giver
  - Product expiration period is assigned by agency to the product packaged in the original container closure
  - In-use compatibility studies conducted for all products
  - Cover the environmental and other in-use factors experienced by the product after the primary CC is breached and any manipulations of the product prior to administration
  - To support administration instructions and storage conditions in the labeling

Product Manipulations

- Typical manipulations for dosage administration
  - Dispersing or crushing of tablets
  - Opening of capsules/mixing with dosing vehicle
  - Mixing original dosage form/crushed dosage form with dosing vehicle (e.g., food, milk, baby formula etc.)

Designing Compatibility Studies

- Test for critical quality attributes that are susceptible to change during manipulation and storage
  - Appearance, assay, impurities, product integrity, dissolution/drug release testing
- Qualify the time and the storage conditions during which the product must be used
- Experience on usability/acceptability of modified product during clinical studies
- These studies should be the basis for use instructions in labeling (e.g., may need to include information if some common foods are not compatible)

Case Study

- Multiple strengths of tablets (low, medium and high)
- Initially proposed to administer crushed tablets mixed with apple puree, water and milk as dosing vehicle
  - Dosing with water and milk to be given through baby bottles or medical syringe
- Testing of crushed tablets with apple puree showed acceptable dose recovery, consistency and stability
- Testing of dosing with milk and water gave relatively low recovery and variable replicate results
  - Baby bottle: water 20.3-42.4%; Milk: 51.1-66%
  - 5 ml Syringe at RT: water 64-83%; Milk 83-93%

Case Study

- Low recovery due to incomplete recovery of drug particles from the dosing vessels (drug particles are suspended in milk and water)
- Additional interactions with the applicant during review process to develop alternative dosing procedure
- New method developed involved obtaining suspension of drug through disintegration of tablet in water
  - Gave acceptable recovery results
  - Approved to be used within 2 hours as opposed to requested 48 hours because lack of assay information and microbiology data for 48 hours
  - Led to detailed preparation procedure in the labeling including, amount of water to be used in the syringe, time to get complete disintegration, rinsing step

Resources

- (Draft): Use of liquids and /or soft foods as vehicle for drug administration: General considerations for selection and in vitro methods for product quality assessmentshttps://www.fda.gov/media/114872/download
- Guidance for Industry: Stability testing of new drug substances and products. https://www.fda.gov/media/71707/download

Questions to Consider

- How do you select dosing vehicles to be studied when dosing vehicle is needed for administration?
- What analytical tests are conducted during dosing vehicle compatibility studies?
  - Physical and chemical stability, extractability, taste/palatability, drug release/bioavailability, dosing accuracy, dose uniformity
- What analytical challenges are faced in conducting these studies?
  - Sample preparations related
  - Analytical procedure/validation related
- Are there any region specific compatibility studies conducted?
- Considerations for including dosing vehicle in the packaging
- How do you select a particular dosage form/dosage strengths?

Thank you!

Questions?