COMMON DEFICIENCIES AND CONSIDERATIONS ON SETTING APPROPRIATE SPECIFICATIONS FOR INTRAVAGINAL RINGS

Kalpana Paudel, Ph.D.

Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
CDER, FDA
June 29, 2022

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Overview

- Introduction
- In vitro release test (IVRT)
- Approaches for setting appropriate in vitro release acceptance criteria
- Common IVRT deficiencies in applications
- Summary

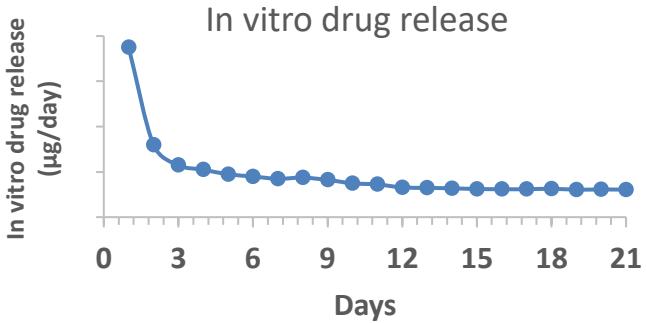
Introduction

- **Vaginal rings are flexible, polymer-based drug-delivery systems for delivery of one or more drugs directly in the vagina**

- **Allows for controlled release of the drug substance over an extended period of time**

- **Can be targeted to achieve a therapeutic effect for**
  - a primarily local site of action with minimal systemic absorption
  - systemic absorption

Release of drug from intravaginal rings



➢ **Phases of drug release**

- **Burst effect or early phase**
- **Transition or middle phase**
- **Late phase**

In Vitro Release Test (IVRT)

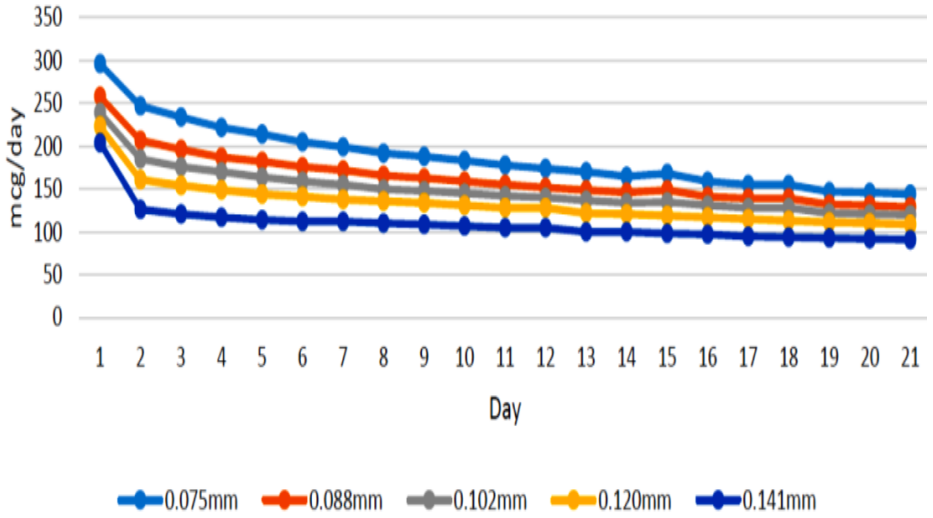
- **Real-time drug release test**
  - evaluated using a release test period that reflects duration of use
  - mechanistic understanding of drug release
- **Accelerated drug release test**
  - can be developed for regulatory purpose
  - establish a relationship between the accelerated and real-time in vitro release tests
  - evidence demonstrating a similar mechanism of drug release of two tests
  - in vitro release data from bio-batch and exhibit batches including stability batches using both real-time and accelerated tests
  - efforts should be made in developing a method that is able to account for at least 80% of the labeled stated amount or when the plateau is reached

In Vitro Release Test (IVRT)

- **IVRT should be discriminating to identified critical attributes that has potential to affect in vitro/in vivo release**
  - Selected method should be able to differentiate the release profiles of the proposed (target) drug product and the test products intentionally manufactured with meaningful variations for the most relevant Critical Bioavailability Attributes (CBAs)

- **Accelerated test should show similar or superior discriminating ability compared to real time testing**
  - recommend evaluating non-conforming batches that are “out of specification” under real-time test conditions

In Vitro Release Test (IVRT)



IVRT Method Validation

- **proposed method should be adequately validated**
- **data should demonstrate robustness, i.e., its capacity to remain unaffected by minor changes in receptor medium temperature, paddle rate, and other test parameters**
- **IVRs may be very sensitive to a change in temperature**
  - a change in temp can give rise to high variability

Setting appropriate acceptance criteria

- **Set clinically relevant acceptance criteria**
  - acceptance criteria that ensure consistent product performance of the formulation compared to that used in the pivotal BE study. Goal of in vitro release testing should be to develop drug product specifications that will ensure adequate performance of future batches prepared within the limits of in vitro release acceptance criteria

- **Set acceptance criteria based on release rate (amount/day)**

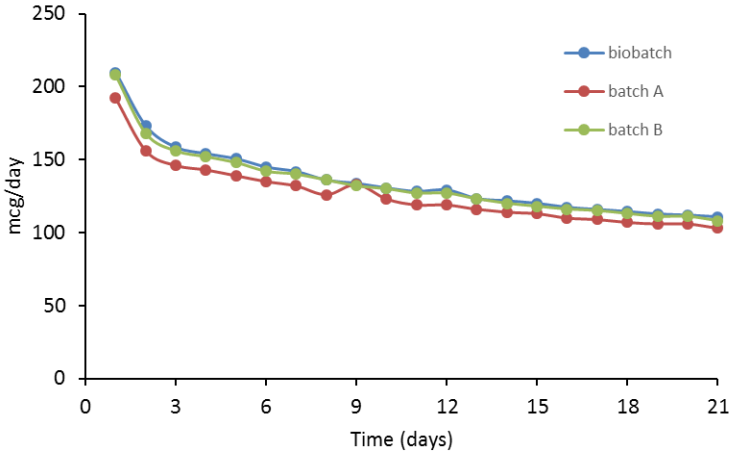
Setting appropriate acceptance criteria

- **Time-points selected for acceptance criteria**
  - **minimum of 3 time points recommended**
  - **time points should cover the early (*burst effect*), middle and late phases of the drug release profile**
  - **sufficient number of samples should be taken to capture these phases**
  - **clearly document the Day the in vitro release data corresponds to**
- **Acceptance criteria range**
  - **should consist of ranges at each proposed sampling point including the first and last time points**

Setting appropriate acceptance criteria

- **When there are no data linking in-vitro drug release and in-vivo performance**
  - **set based on data of the clinical batch(es)**
  - **n=12 units**
  - **drug release acceptance ranges are based on mean target value ±10% at steady state**
  - **wider acceptance criteria limits may be acceptable if supported by a safe space approach**

Example: Setting acceptance criteria



Proposed acceptance criteria

- Day 1: NMT 360 µg/day/ring

The individual daily amounts released meet the stated limit

- Days 2-21: Mean 96-144 µg/day/ring

The mean should be within the specification range

- Day 21: NLT 80 µg/day/ring

The individual daily amounts released meet the stated limit

Recommendation: Establish in vitro daily release range for key stages

- Day 1 (burst release)
- A single day in transition state (Day 5)
- A single day in steady state (Day 14)
- Day 21

Example: Setting acceptance criteria

Day 1: 195-245 µg/day

Day 6: 118-145 µg/day

Day 16: 100-125 µg/day

Day 21: 91-115 µg/day

Setting Acceptance Criteria

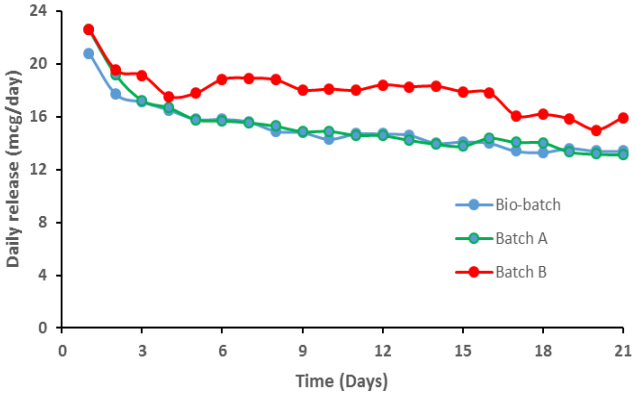
Safe space is established by defining the extremes of in vitro release rate (bracket) within which drug product variants are bioequivalent to each other and to the target or reference formulation (e.g., clinical trial formulation).

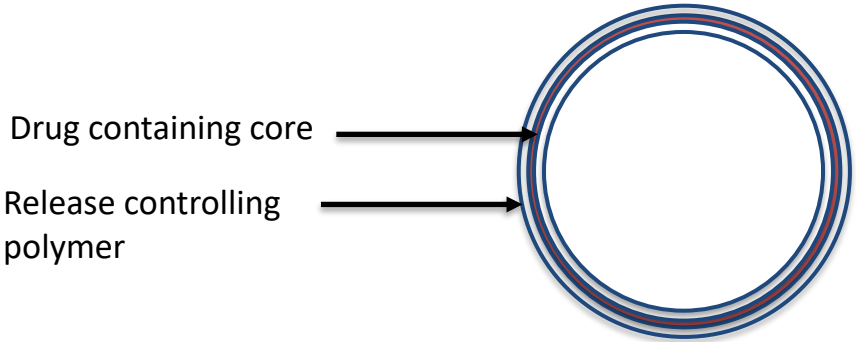
Setting Acceptance Criteria

- **Safe-space based on bracketing approach**
  - Limits are established based on demonstration of BE between upper and lower proposed bounds

- **Safe space built based on modeling and simulation**
  - Physiologically based biopharmaceutics modeling
  - IVIVC modeling

Example: Setting Acceptance Criteria





- Batch B with skin thickness 70 µm has faster daily release rate than the biobatch
- There are no data to evaluate if Batch B and bio-batch will have comparable in vivo performance
- A safe space can provide opportunity to understand the product and make an informed decision to set clinically relevant acceptance criteria

Common Deficiencies

- **Method development report not included in the application**
  - Data demonstrating that the selected method is appropriate for the proposed drug product; method should be product specific
  - Validation of in vitro release method
- **Failure to demonstrate that the method is discriminating**
  - Identify Critical Bioavailability Attributes and submit data obtained from batches with intentional meaningful changes to these variables
  - Conduct appropriate statistical test comparing in vitro release profile of the changed vs target batch (bio-batch)
- **Data do not support the proposed acceptance criteria**
  - Acceptance criteria should be based on the data obtained from the proposed product
  - Include time points to represent different phases of release
  - Consider ranges as acceptance criteria limit rather than NLT or NMT for all time points
  - Submit complete in vitro release profile data that includes individual and mean values in graphical and tabulated form for the pivotal BE batches and relevant exhibit and stability batches

Summary

- **Develop an appropriate product specific *in vitro* drug release test**
  - consider developing an appropriate accelerated in vitro release test
  - data demonstrating that the selected method is appropriate for the product
  - demonstration of discriminating power

- **Set clinically relevant acceptance criteria based on**
  - data obtained from batches used in clinical studies
  - establishing a safe space via modeling and simulation/bracketing approach

Acknowledgements

- Vidula Kolhatkar, Ph.D.
- Om Anand, Ph.D.
- Tapash Ghosh, Ph.D.
- Okpo Eradiri, Ph.D.
- Bhagwant Rege, Ph.D.
- Division of Biopharmaceutics

Thank you!