Considerations on In Vitro Drug Release Testing for Long Acting Drug Products for Quality Control

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Overview

- In vitro release test (IVRT)
- Current approach
  - Product specific in vitro release test
  - Discriminating ability
  - Acceptance criteria
- Common deficiencies
- Moving forward
- Summary

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

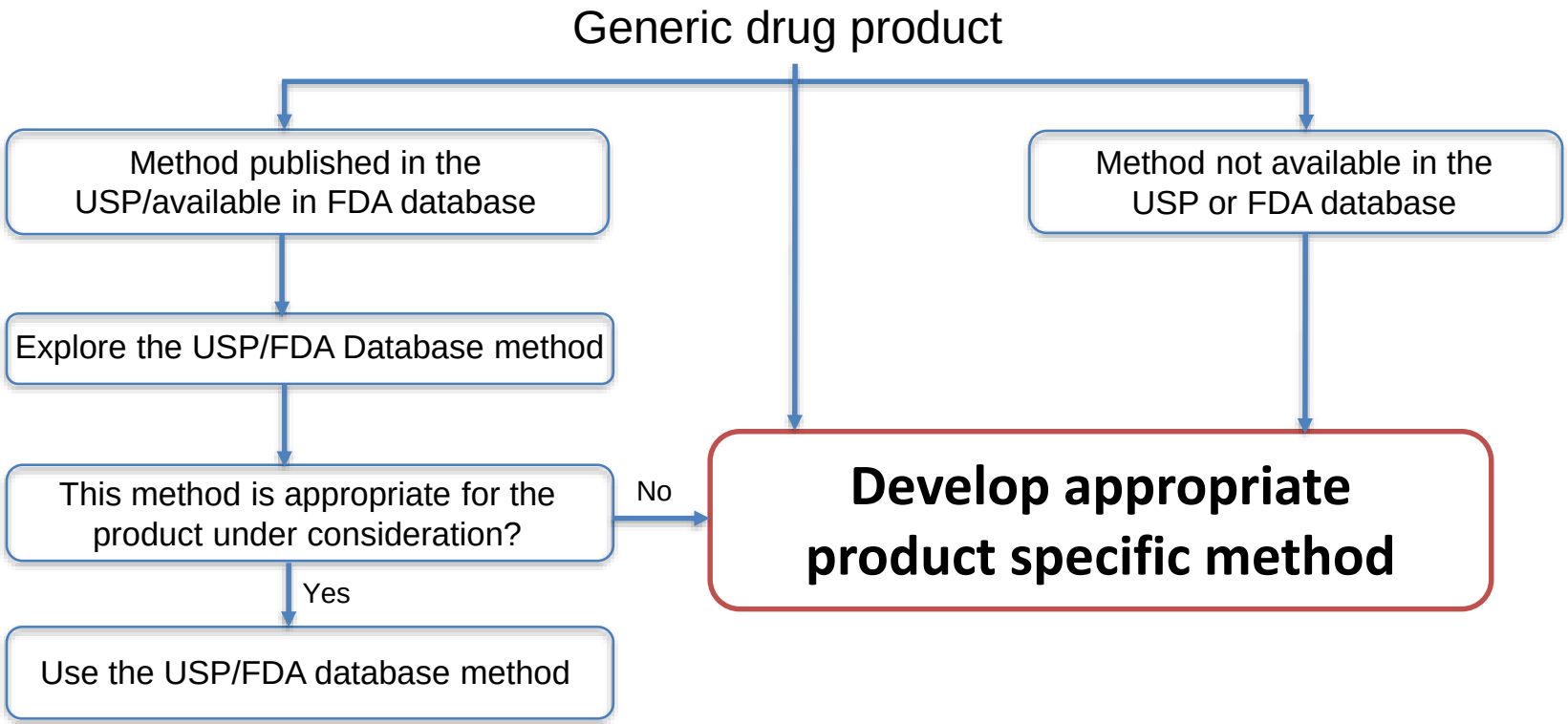
assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

In vitro drug release specifications

- Method and acceptance criteria
  - Purpose of in vitro drug release specifications from the quality perspective
    - Detect variations during routine product manufacturing
    - Detect changes during product storage that may negatively impact product performance
    - Support minor/moderate CMC changes

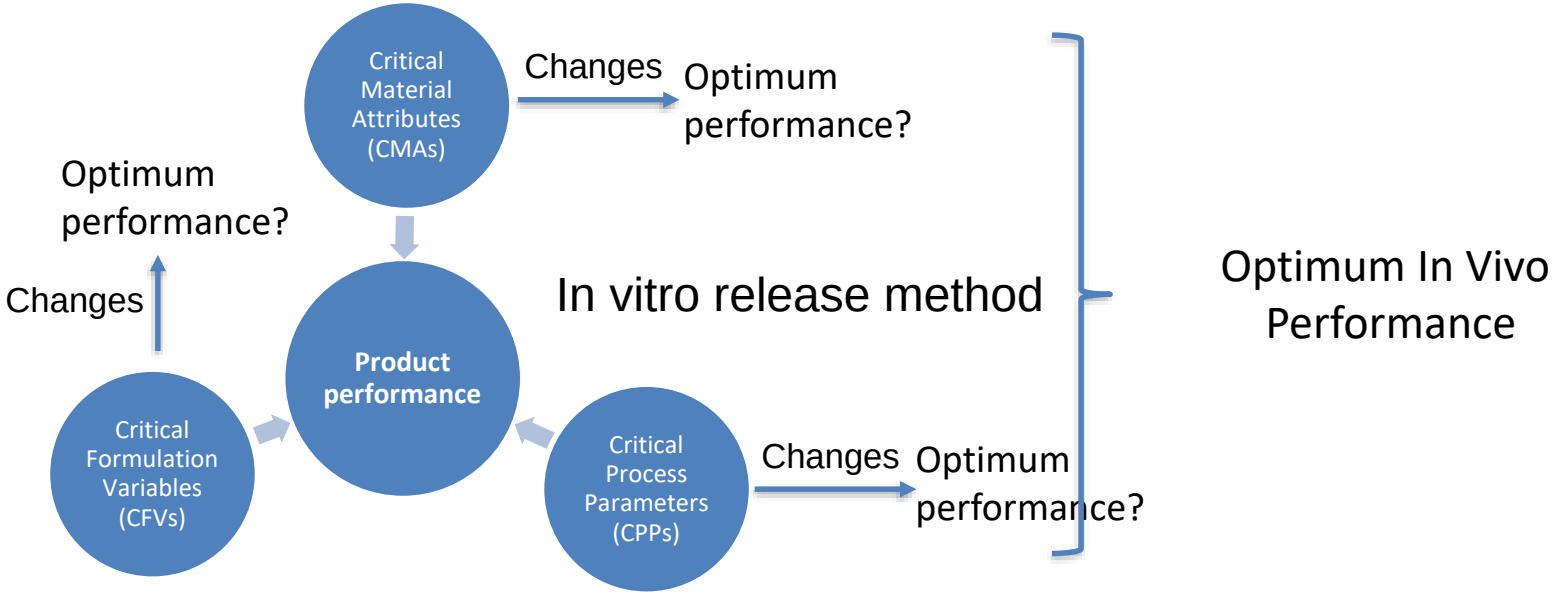
Current approaches to develop an in vitro release method



Challenges in complex products

- Complex formulations and excipients
- Small changes in excipient or manufacturing process may lead to significant changes in product release
  - Identification of CMAs, CPPs and CFVs is crucial

Challenges in complex products, cont.



Considerations for product specific method development

- Identification of appropriate testing conditions
- Discriminating ability
- Selection of acceptance criteria

Consider CMAs, CPPs and CFVs and how these affect in vitro release and product performance when developing a product specific method

Identification of testing conditions

In vitro drug release test is a key critical quality attribute (CQA)

- pH solubility profile of the API
- Selection of the apparatus
  - Use of non-compendial apparatus
- In vitro release media
- Validation

Additional considerations

- **Real-time testing**: In vitro drug release evaluated through the intended period of product use to gain mechanistic understanding of drug release
- **Accelerated short-term release test**: can be developed for regulatory purpose supported by appropriate cross-validation demonstrating the interchangeability of the proposed tests as quality control tool

Discriminating ability

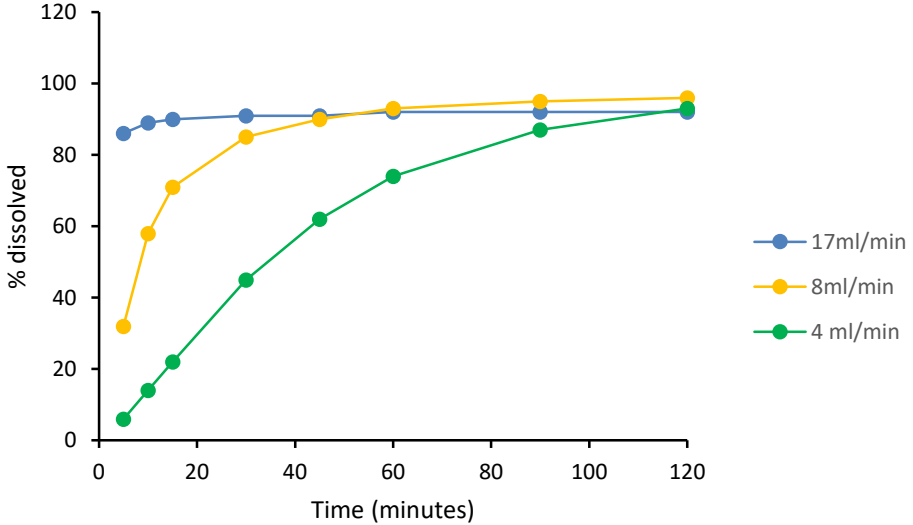
- A discriminating in vitro release method can differentiate drug product batches manufactured under target conditions from those batches manufactured with meaningful variations for the most relevant manufacturing variables
  - Meaningful variations: ± 10-20% change to the specified values or ranges for the critical variables
- Use all available CMC, in vitro release and in vivo PK data
- Selection of appropriate acceptance criteria helps in improving discriminating ability

Setting Acceptance Criteria

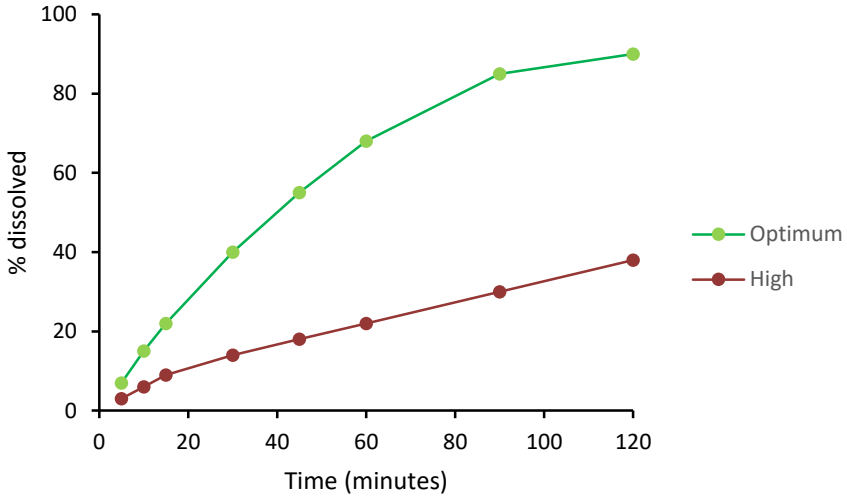
- Set based on data of the pivotal clinical/PK drug product-batches and exhibit batches
  - Data from n = 12 units of bio-batch and exhibit batches
  - Consider available data for drug products used in failed and acceptable BE studies
- A minimum of three time points is recommended to set the acceptance criteria. These time points should cover the early, middle, and late stages of the drug's release profile.
  - The last time point should be where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.
  - In general, the selection of the dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider acceptance criteria limits may be acceptable if they are supported by a safe space approach.

Example: optimizing in vitro release method

- Injectable suspension with low solubility API



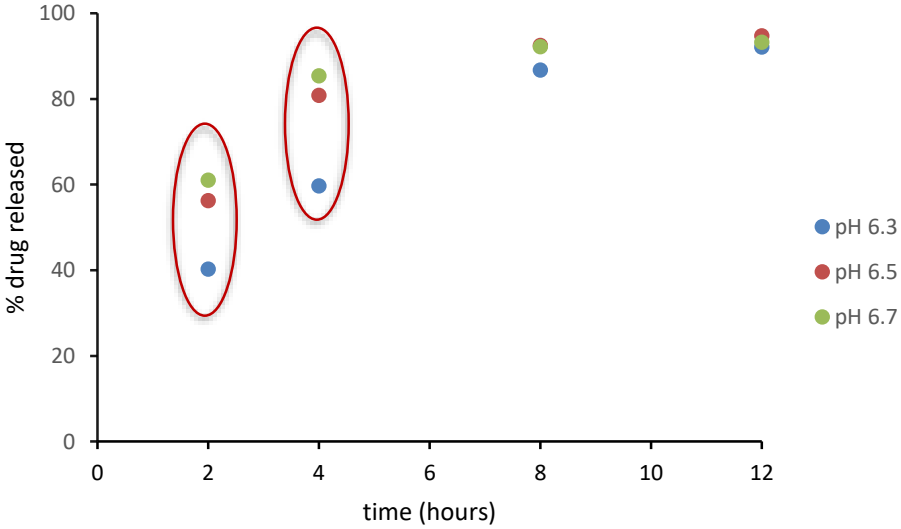
In vitro release observed using different flow rates in USP apparatus IV



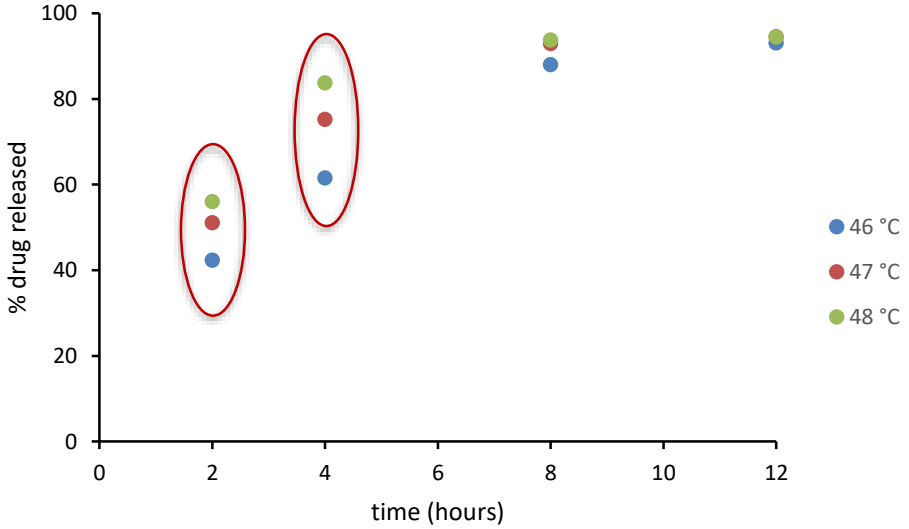
In vitro release observed for product with optimum PSD and higher than optimum PSD

Special considerations

- Method validation
- Effect of pH



- Effect of temperature



Common deficiencies and recommendations

- Method development and validation report
  - Data demonstrating that the selected method is appropriate for the proposed drug product
  - Validation of in vitro release method
- Demonstration of discriminating ability
  - Identify critical manufacturing variables and submit data obtained from batches with intentional meaningful (10-20%) changes to these variables
  - Conduct appropriate statistical test (e.g. similarity factor f2) comparing in vitro release profile of the changed vs target batch
- Appropriate acceptance criteria
  - Acceptance criteria should be based on the data obtained from the proposed product
  - Consider ranges as acceptance criteria limit rather than NLT or NMT when there is more than one time-point

Moving forward…

- Clinically relevant drug product specifications (CRDPS)
  - CRDPS are those specifications that ensure consistent product performance for the marketed product relative to those achieved by the clinical trial formulation
- 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 acceptable in vitro release specifications

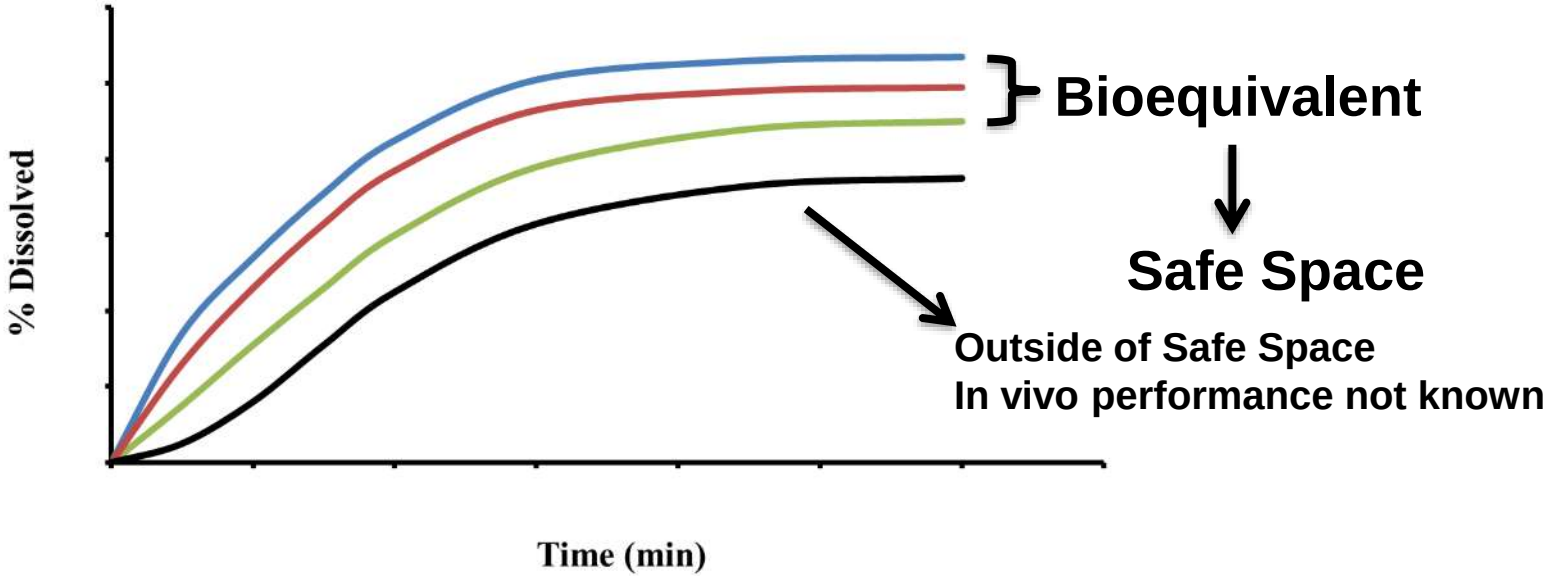
Moving forward: CRDPS

- Understanding impact of changes in critical quality attributes on in vitro release and systemic exposure to establish “Safe Space”
- Safe space: space within which the proposed in vitro release specifications (i.e., method and acceptance criteria) are demonstrated to be biopredictive/clinically relevant.

Moving forward: Safe Space

- Based on pilot and pivotal BE studies
  - Identify extremes of dissolution profile for products that are found to be BE to one another and the reference listed drug. Future batches with profiles between these extremes can be considered BE.
- Based on a validated in vitro in vivo correlation (IVIVC) established via conventional approaches
- Based on in vitro in vivo relationship (IVIVR) or IVIVC established via a verified physiologically based biopharmaceutics model (PBBM)
  - Identify a range of virtual dissolution profiles within which the drug product batches are found to be bioequivalent to one another and the RLD (e.g., via virtual BE analysis).
  - The virtual range of dissolution profiles should contain the target dissolution profile of generic product and the RLD.
  - All batches with in vitro release profiles falling within the safe space are expected to be BE to one another and the RLD.

Moving forward: Safe Space



Summary

- Product specific method
  - Data demonstrating that the selected method is appropriate for the product
  - Identifying CMAs, CPPs and CFVs
  - Demonstration of discriminating ability
- Data driven acceptance criteria
  - Acceptance criteria based on observed data (i.e. biobatch) to ensure similar product performance
- Clinical relevance
  - In vitro release testing to ensure product performance
  - Establishing “Safe Space”

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