

In Vitro Release Test (IVRT) for In Situ Gel/Depot-Forming Drug Products

Agm (Abu) Mostofa, Ph.D.

Staff Fellow, Division of Bioequivalence I
Office of Bioequivalence, Office of Generic Drugs
CDER | U.S. FDA

**Advancing Generic Drug Development 2024:
Translating Science to Approval**
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Learning Objectives

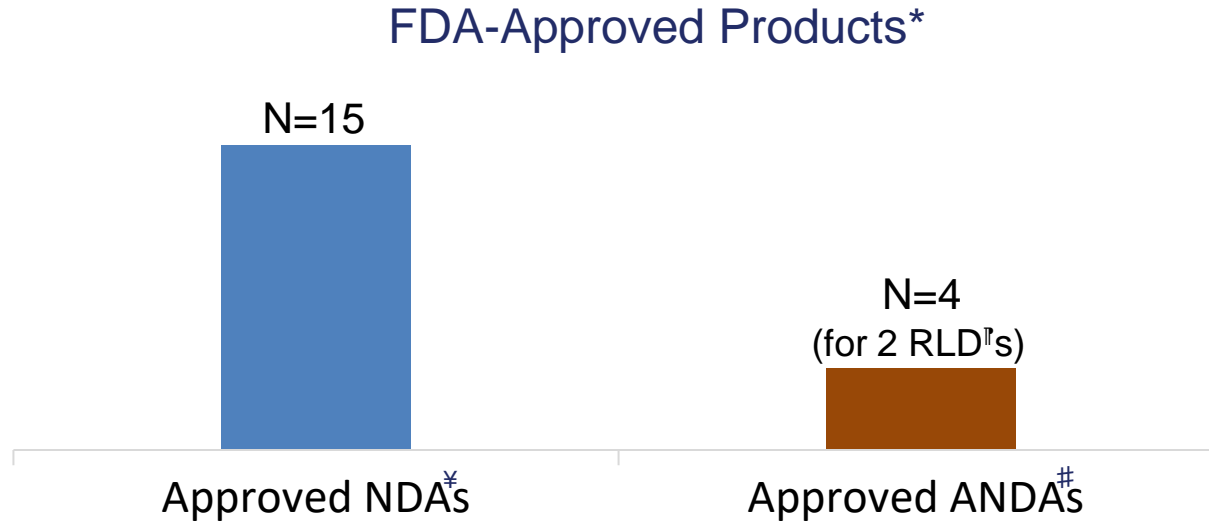


- Related to IVRT study for in situ gel/depot-forming drug products:
 - Identify challenges in IVRT method development
 - Explain key considerations in IVRT method development and validation
 - Describe submission contents for an IVRT study

In Situ Gel/Depot-Forming Drug Products



- In situ gel/depot-forming drug products are formulations that form a gel/depot at the administration site and exhibit prolonged drug delivery.



^ℙRLD: Reference Listed Drug; [¥]NDA: New Drug Application; [#]ANDA: Abbreviated New Drug Application

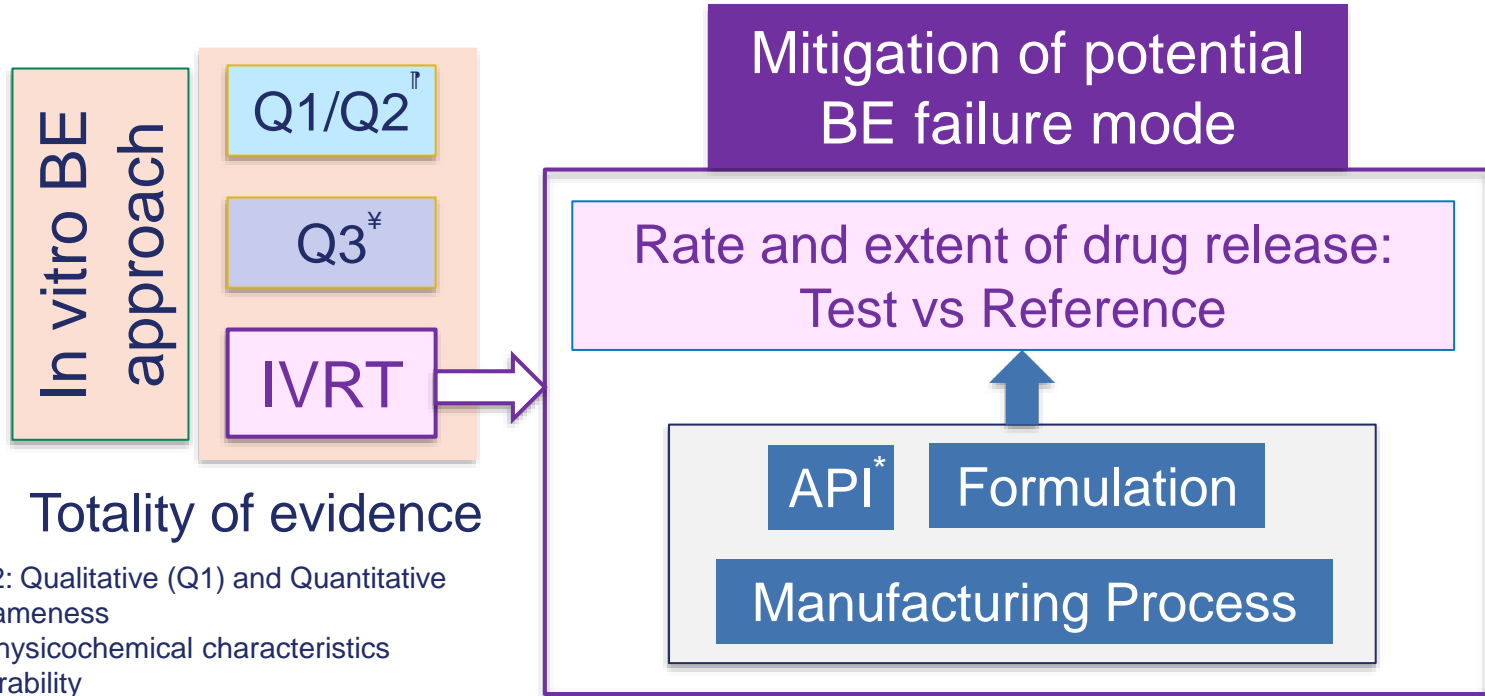
Overview of Product-Specific Guidance (PSG) Recommendations



In situ gel/depot-forming drug products	In vivo BE* study(s)	In vitro BE approach	IVRT study
Degarelix Acetate Subcutaneous Powder (RLD: NDA 022201)	No	Yes	Yes
Lanreotide Acetate Subcutaneous Solution (RLD: NDA 022074)	Yes	Yes	Yes
Leuprolide Acetate Subcutaneous Powder (RLD: NDA 021343)	Yes	No	
Leuprolide Acetate Subcutaneous Powder (RLD: NDAs 021379 and 021488)	Yes	No	
Leuprolide Acetate Subcutaneous Powder (RLD: NDAs 021731 and 213150)	Yes	No	
Leuprolide Mesylate Subcutaneous Emulsion (RLD: NDA 211488)	Yes	No	
Buprenorphine Extended Release (ER) Subcutaneous Solution (RLD: NDA 209819)	Yes	No	
Risperidone for ER Subcutaneous for Suspension (RLD: NDA 210655)	Yes	No	
Doxycycline Hyclate ER Periodontal System (RLD: NDA 050751)	Yes	Yes	Yes
Bupivacaine ER Infiltration Solution (RLD: NDA 204803)	Yes	Yes	Yes
Timolol Maleate Gel Forming/Drops Ophthalmic Solution (RLD: NDA 020330)	No	Yes	No

*BE: Bioequivalence

IVRT Study: Purpose



[†]Q1/Q2: Qualitative (Q1) and Quantitative (Q2) sameness

[‡]Q3: Physicochemical characteristics comparability

^{*}API: Active pharmaceutical ingredient

Challenges in IVRT Method Development



- Lack of compendial method
- No specific recommendation of study conditions in the PSGs
- Demonstration of discriminatory ability
- Additional step compared to other products:
Gel/depot formation
 - Optimization of gel/depot inducing conditions

How to Address These Challenges?

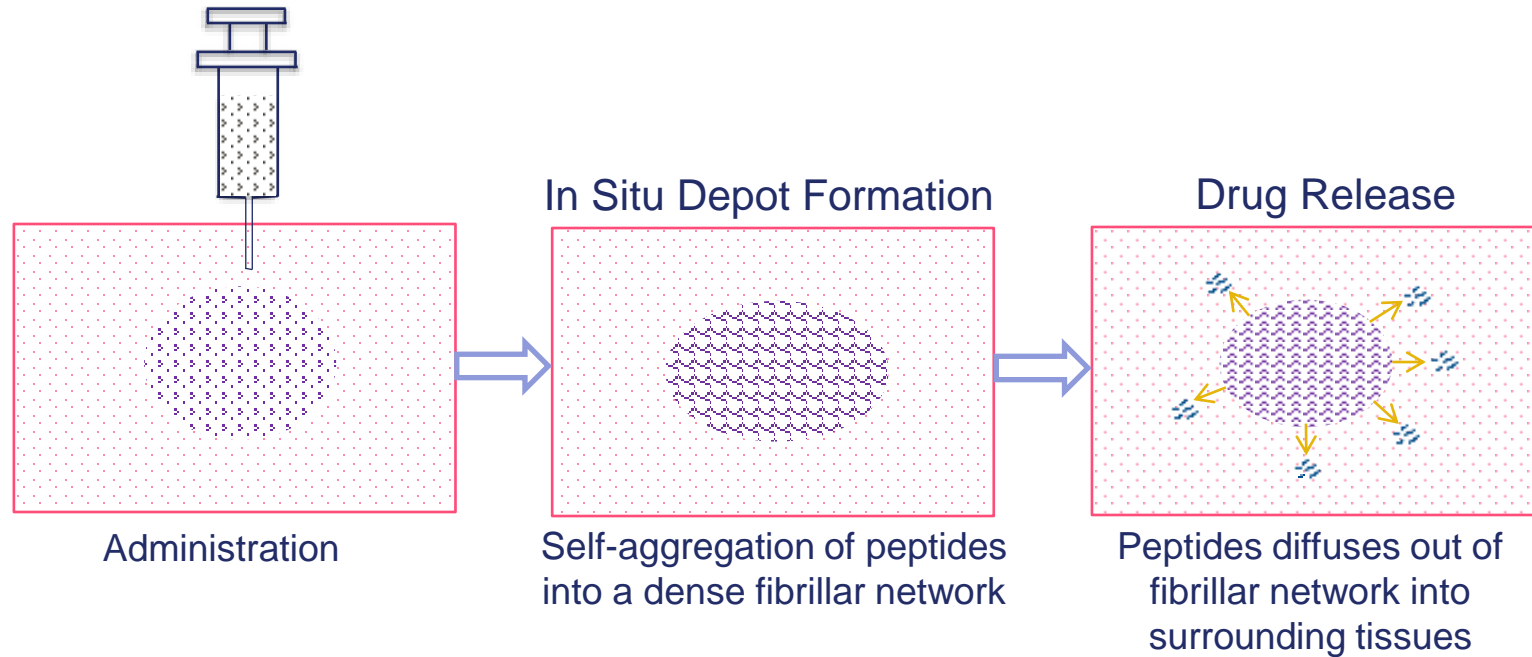


Understand the mechanism of depot formation and drug release

Examples:

- Self-Aggregating Peptide Drugs: Upon administration, peptides self-aggregate to form a gel/depot, enabling prolonged drug release.
- Polymer-Based Formulations: Upon administration, polymers precipitate with the drug to form a gel/depot, allowing for prolonged drug release.

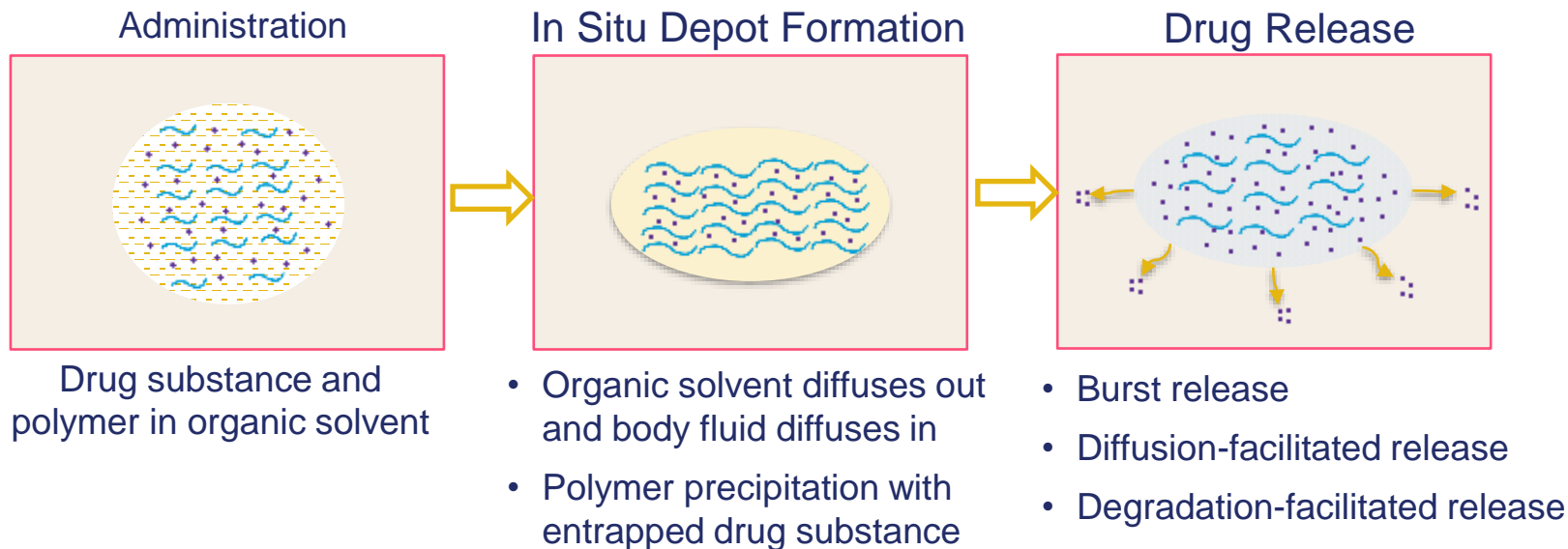
Self-Aggregating Peptide Drugs



References:

- <https://pubmed.ncbi.nlm.nih.gov/35787229/>
- <https://pubmed.ncbi.nlm.nih.gov/28944744/>
- <https://www.sciencedirect.com/science/article/abs/pii/S1773224724006658>

Polymer-Based Formulations



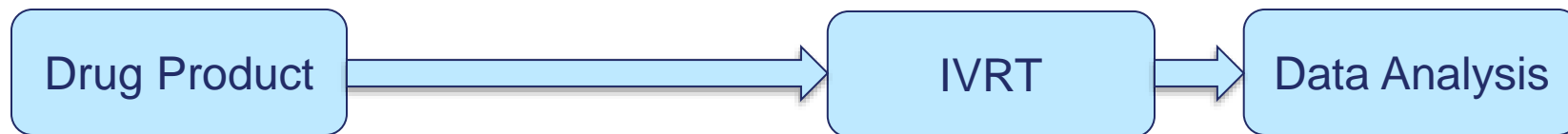
Reference:

- <https://pubmed.ncbi.nlm.nih.gov/35976565/>
- <https://pubmed.ncbi.nlm.nih.gov/37422267/>
- <https://pubmed.ncbi.nlm.nih.gov/34363860/>

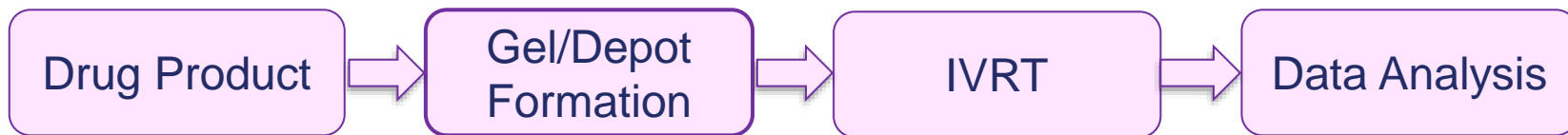
IVRT for In Situ Gel/Depot-Forming Products



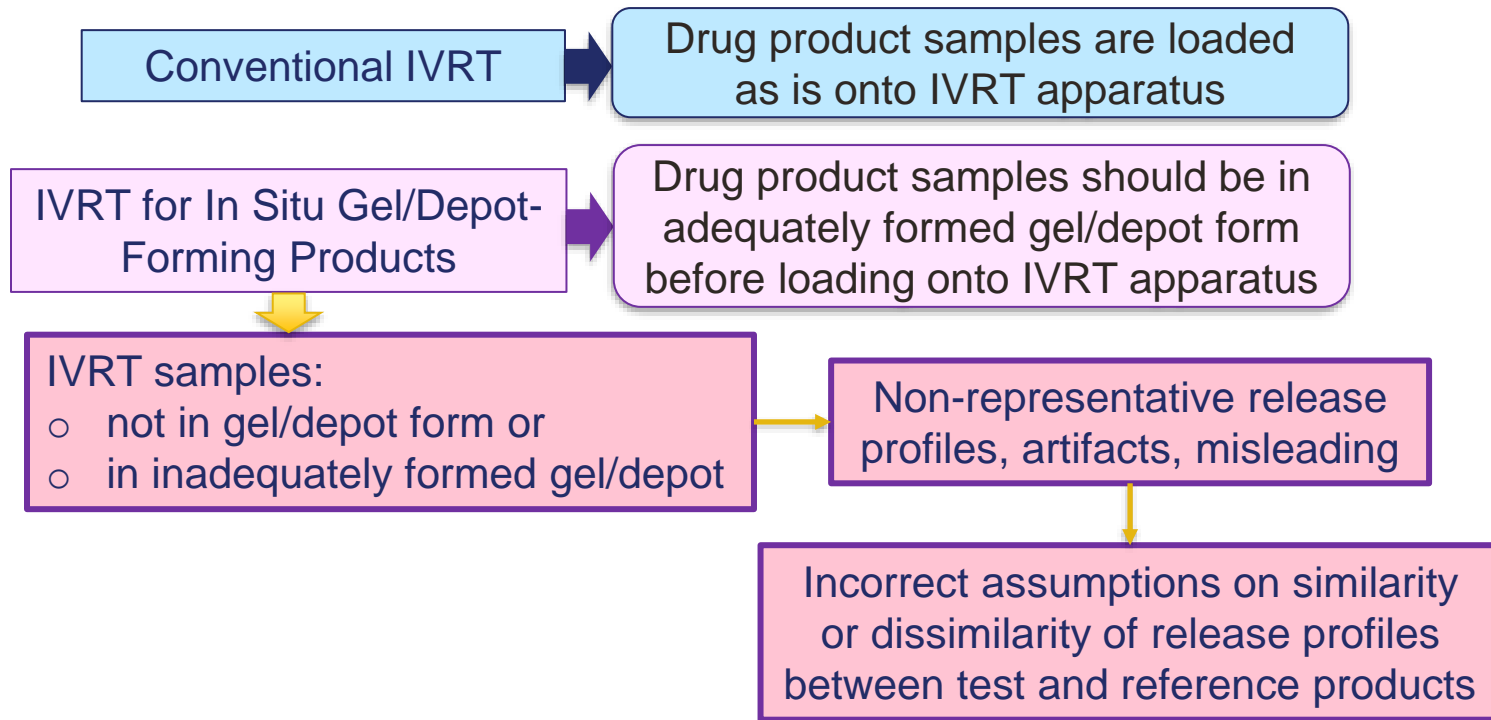
IVRT in General



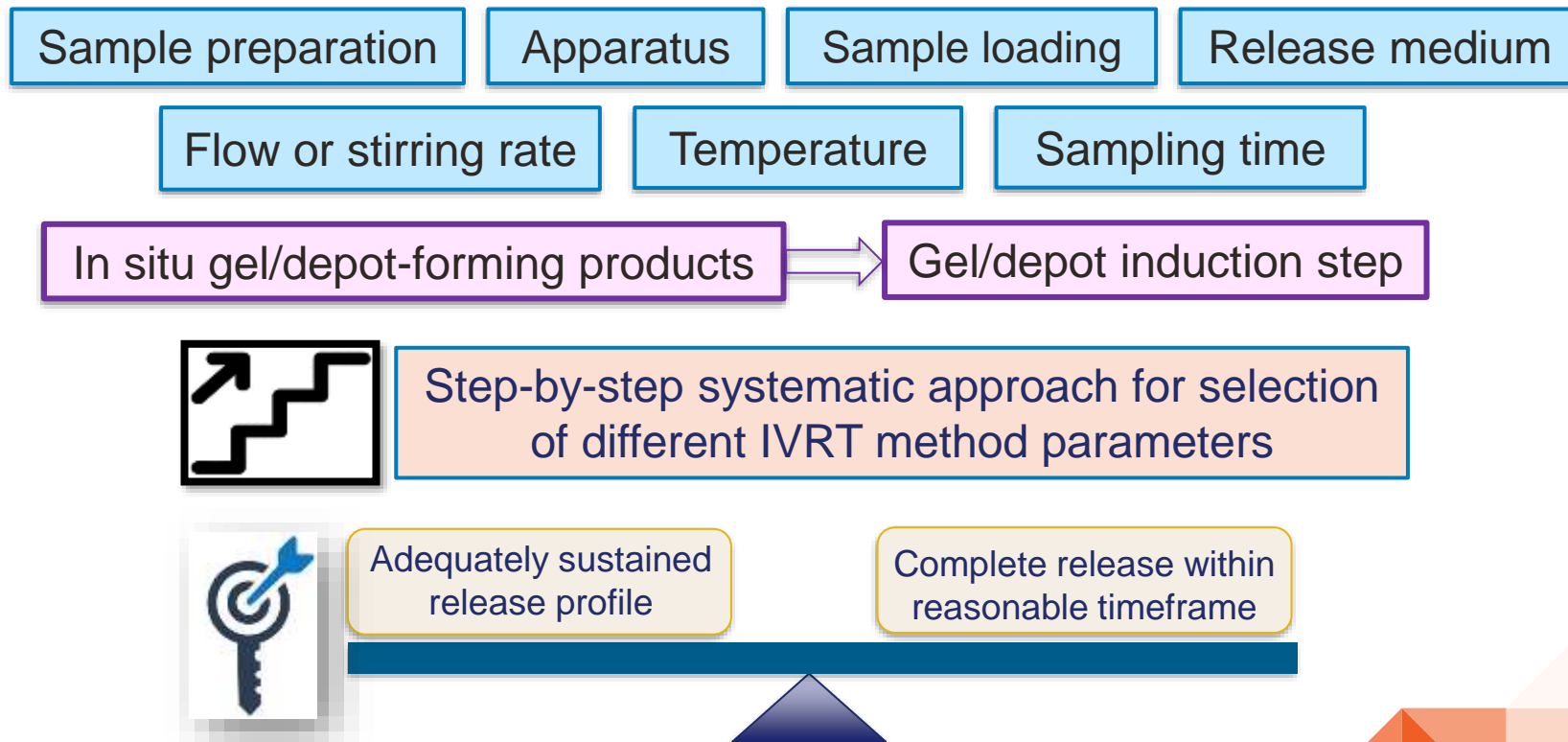
IVRT for In Situ Gel/Depot-Forming Products



A Distinct IVRT Method Parameter for In Situ Gel/Depot-Forming Products: Induction of Gel/Depot Formation



Key Parameters of IVRT Method Development



Gel/Depot Inducing Conditions: Key Considerations



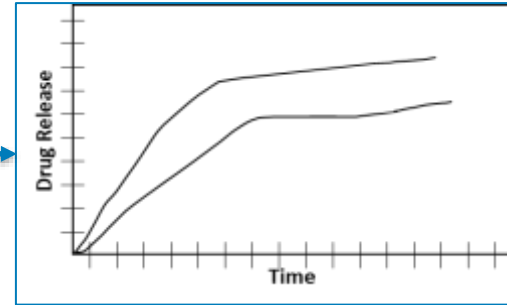
- Take an exploratory approach: Investigate factors influencing the gel/depot formation process
- Explore various gel/depot-inducing conditions, including physiologically relevant ones
 - Depending on the drug product:
 - Sample amount
 - Gel/depot-inducing media
 - Sample-to-media ratio
 - Incubation temperature and time
- Assess consistency and reproducibility of gel/depot formation

IVRT Method Validation: Key Considerations



- Robustness
- Discriminatory ability

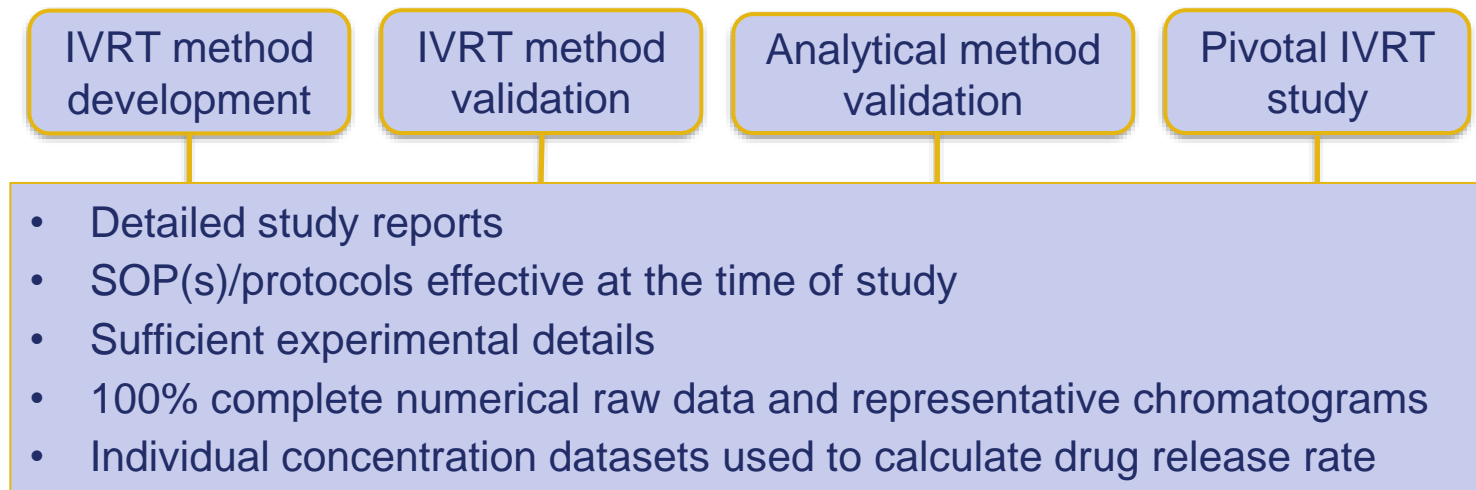
Differentiation of experimental non-BE test formulations



In situ gel/depot-forming products

Discriminatory ability: Critical formulation and manufacturing process attributes that can affect gel/depot formation and drug release kinetics

IVRT Study Related Submission Content in an ANDA



Typical Deficiencies in IVRT Study of In Situ Gel/Depot-Forming Drug Products



- Gel/depot induction step was not included in the IVRT method.
- Thorough exploration of gel/depot induction under various conditions, including physiologically relevant conditions, was not conducted.
- Justification and supporting data provided for selected gel/depot inducing conditions were inadequate/incomplete.
- Gel/depot formation was inconsistent and irreproducible, potentially contributing to high variability in release profiles.
- Critical formulation and manufacturing attributes affecting gel/depot formation and drug release were not considered during the evaluation of discriminatory ability.

SUMMARY



- Gel/depot formation is a crucial step in the IVRT method for in situ gel/depot-forming drug products.
- Conduct a thorough exploration of gel/depot-inducing conditions, including physiologically relevant conditions.
- Aim to achieve a well-formed, consistent, and reproducible gel/depot to ensure a reliable and sustained in vitro drug release profile.
- Optimize the IVRT method parameters based on the understanding of depot formation and the drug release mechanism.
- During the evaluation of discriminatory ability, consider the critical attributes related to formulation and manufacturing process that can affect gel/depot formation and drug release.

Challenge Question #1

Which of the following statements about IVRT for in situ gel/depot-forming products are true? Select all that apply.

- A. Understanding of gel/depot formation and drug release mechanism is important for IVRT method development.
- B. In vitro BE approach involves only IVRT study.
- C. During IVRT method development for in situ gel/depot-forming products, additional consideration should be given to gel/depot-forming step.
- D. Specific IVRT apparatus are available for in situ gel/depot-forming products.
- E. IVRT study is not needed if the test formulation is Q1/Q2 to the RLD.

Challenge Question #2

Which of the following statements about IVRT for in situ gel/depot-forming products are false? Select all that apply.

- A. An adequate IVRT method should mimic the exact in vivo release profile.
- B. Selection of release medium should be based on the solubility and stability of the drug in the release medium.
- C. IVRT method validation involves demonstration of method robustness and discriminatory ability.
- D. Missing study protocols/SOPs may warrant a BE deficiency.
- E. IVRT method validation is the same as the analytical method validation.

Acknowledgements



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Assessment Teams