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

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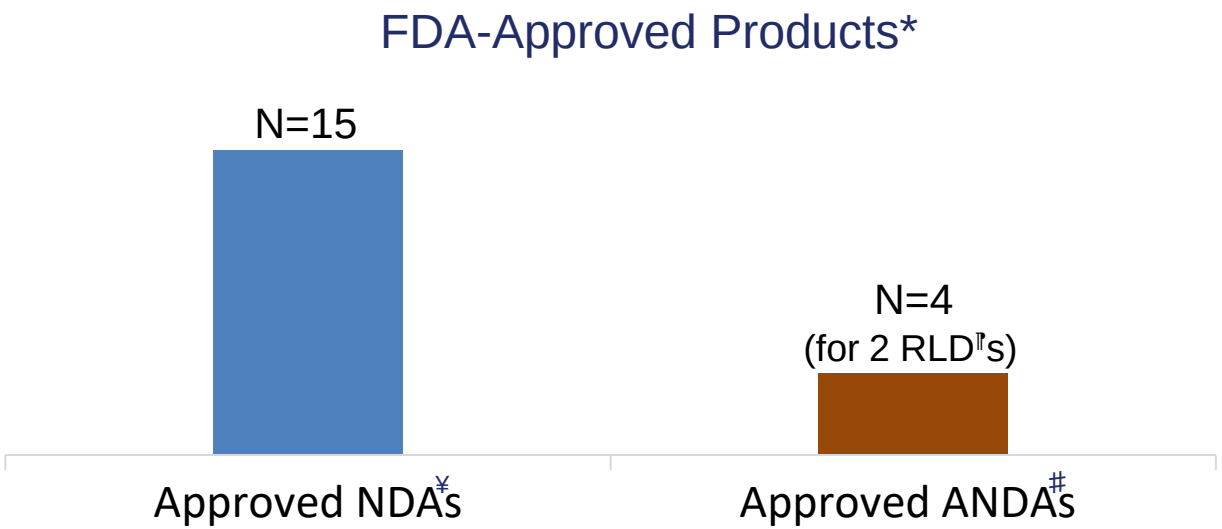
Learning Objectives

- 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.



ⁱRLD: Reference Listed Drug; ¥NDA: New Drug Application; #ANDA: Abbreviated New Drug Application

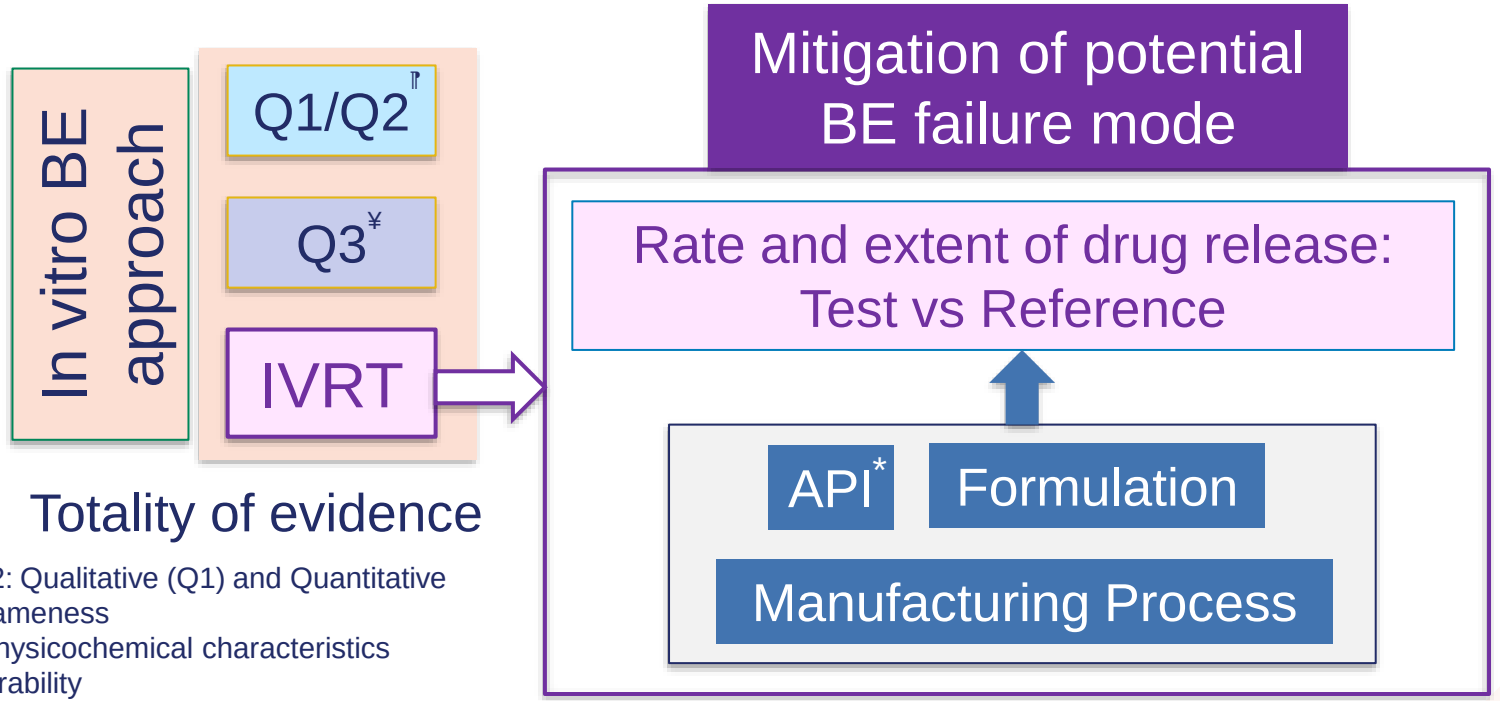
*Source: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

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



ǂQ1/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

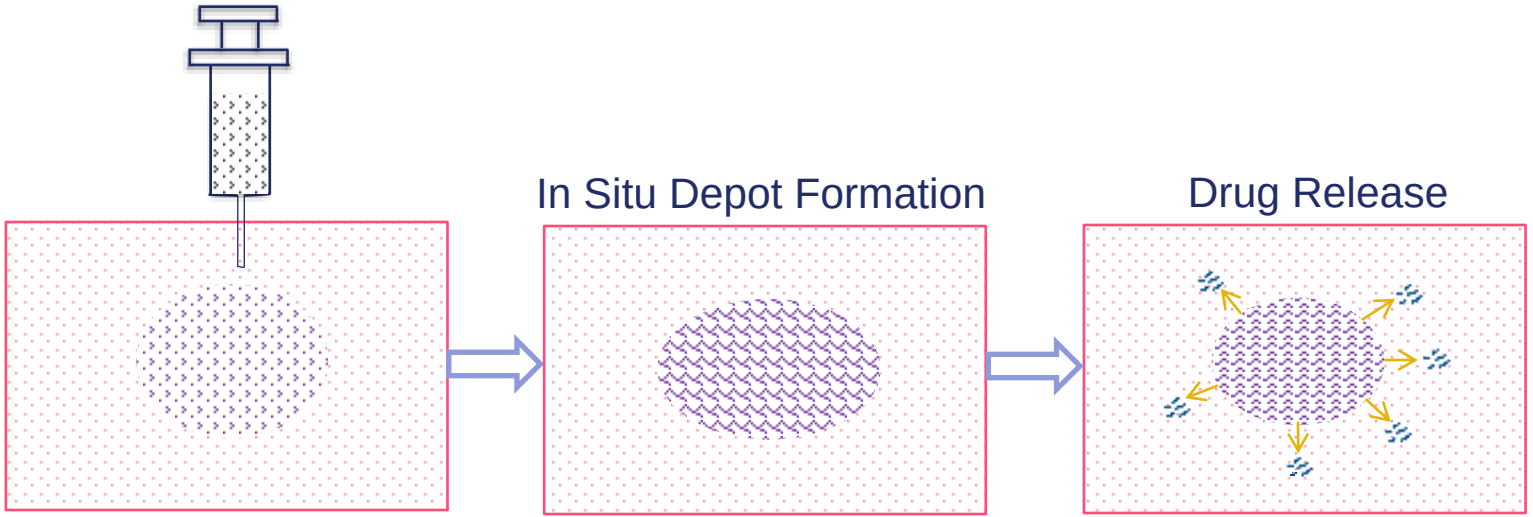
How to Address These Challenges?

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

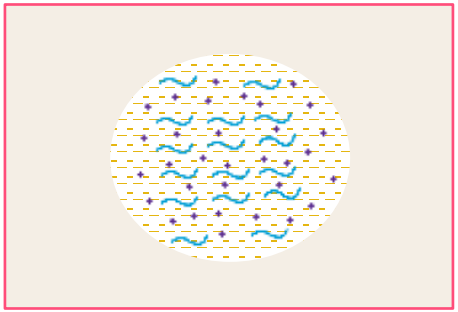


References:

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

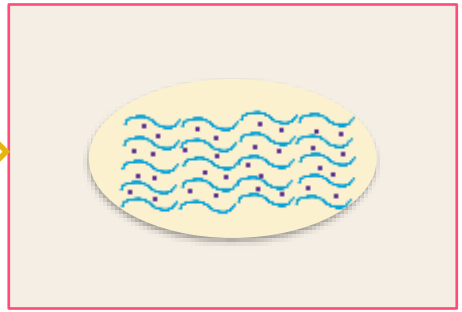
Polymer-Based Formulations

Administration



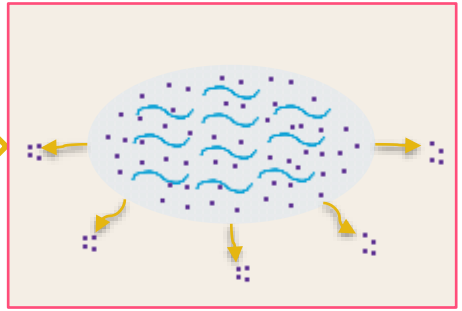
Drug substance and polymer in organic solvent

In Situ Depot Formation



- Organic solvent diffuses out and body fluid diffuses in
- Polymer precipitation with entrapped drug substance

Drug Release



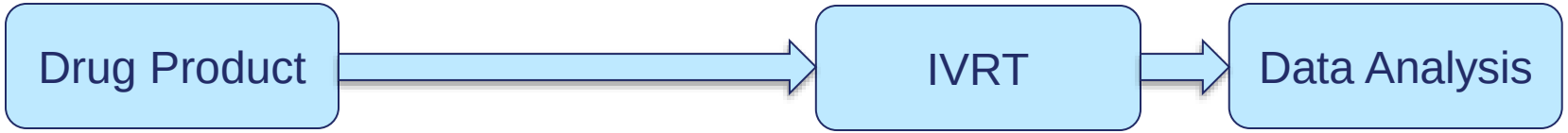
- Burst release
- Diffusion-facilitated release
- Degradation-facilitated release

Reference:

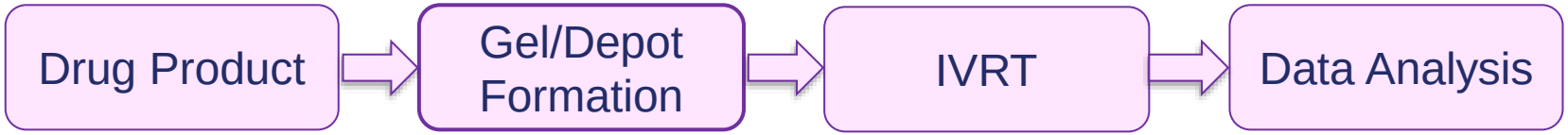
- https://pubmed.ncbi.nlm.nih.gov/35976565/
- https://pubmed.ncbi.nlm.nih.gov/37422267/
- https://pubmed.ncbi.nlm.nih.gov/34363860/

IVRT for In Situ Gel/Depot-Forming Products

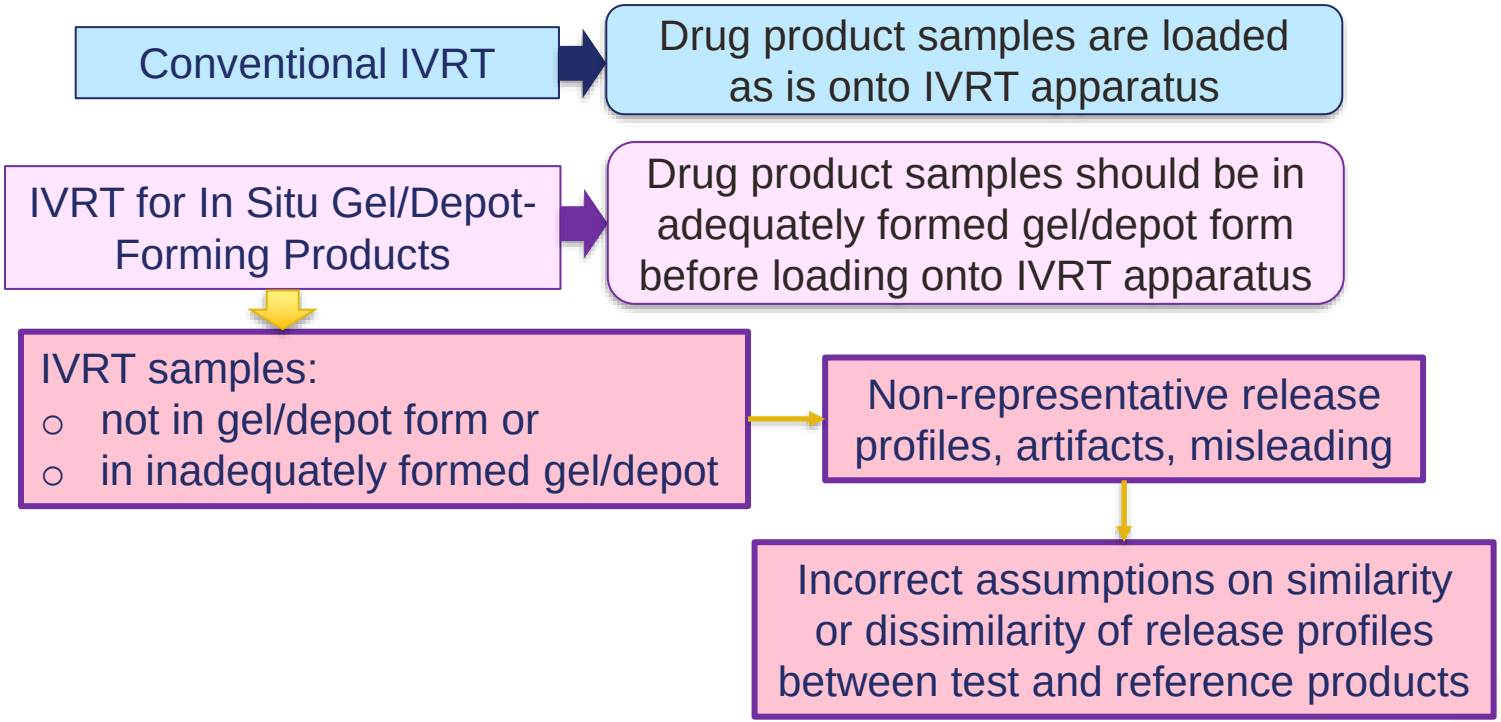
IVRT in General



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

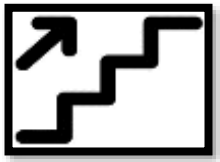


Key Parameters of IVRT Method Development

Sample preparation | Apparatus | Sample loading | Release medium

Flow or stirring rate | Temperature | Sampling time

In situ gel/depot-forming products → Gel/depot induction step



Step-by-step systematic approach for selection of different IVRT method parameters

Adequately sustained release profile

Complete release within reasonable timeframe

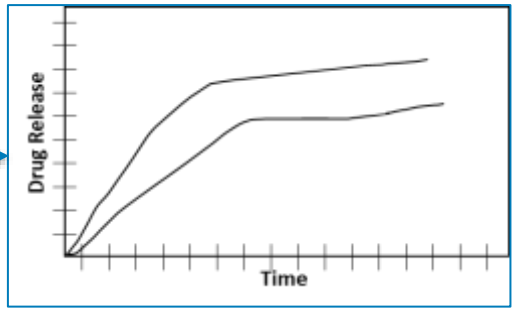
Gel/Depot Inducing Conditions: Key Considerations

- 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

IVRT method development | IVRT method validation | Analytical method validation | Pivotal IVRT study

- Detailed study reports
- SOP(s)/protocols effective at the time of study
- Sufficient experimental details
- 100% complete numerical raw data and representative chromatograms
- Individual concentration datasets used to calculate drug release rate

Incomplete information → Deficiencies → Delayed approval

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.

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Assessment Teams