Regulatory Uses of IVRT Studies on Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products

FDA-CRCG Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted products

Virtual Public Workshop

Bin Qin

Staff Fellow

Office of Research of Standards, OGD

CDER | U.S. FDA

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Outline

- IVRT for bioequivalence (BE) purpose
- IVRT for quality control (QC) purpose
- In vitro-in vivo correlation (IVIVC)

Role of IVRT

- In vitro drug release tests are in vitro tests that measure the rate and extent of dissolution or release of drug substance from a drug product under a specific condition.
- IVRT should be a discriminating test that is responsive to physicochemical changes in drug products, such as
  - Drug substance: polymorphic form, aggregate/co-aggregate structure
  - Excipient: grade/source, amount
- IVRT is an important quality control tool used for monitoring drug stability and consistency of manufacturing process, such as
  - Location and/or structural arrangement of formulation components
  - Particle size, viscosity, non-equilibrate higher energy states

IVRT for BE Purpose

- IVRT is a valuable tool for demonstrating comparative in vitro drug release rate/profiles between test and reference products.
- IVRT for BE determination is one component of a totality of evidence approach.
- For BE purpose, IVRT is used
  - as part of an in vitro only BE approach, or
  - in conjunction to an in vivo study to support BE, or
  - to support waiver of in vivo BE study for other strengths (if applicable)

IVRT for BE Purpose
Example Complex Ophthalmic Drug Products

Route; dosage form	Active ingredient, strength	Uses of IVRT
Ophthalmic; ointment	• Acyclovir, 3% • Bacitracin, 500 units/gram • Ciprofloxacin hydrochloride, EQ 0.3 base • Erythromycin, 0.5% • Loteprednol etabonate, 0.5%	In vitro only BE option is available in these PSGs[1]; IVRT is used as part of the in vitro only BE approach
Ophthalmic; emulsion	• Cyclosporine, 0.05% • Difluprednate, 0.05%	
Ophthalmic; gel	• Loteprednol etabonate, 0.38%, 0.5%	
Ophthalmic; suspension	• Besifloxacin hydrochloride, EQ 0.6% base • Dexamethasone; Neomycin sulfate; Polymyxin B sulfate, 0.1%|EQ 3.5 mg base/mL|10,000 units/mL • Dexamethasone; Tobramycin, 0.05%|0.3%, 0.1%|0.3% • Fluorometholone, 0.1%, 0.25% • Fluorometholone Acetate, 0.1% • Loteprednol etabonate, 0.2%, 0.5%,1% • Loteprednol etabonate; Tobramycin, 0.5%|0.3% • Nepafenac, 0.1%, 0.3% • Prednisolone acetate, 1%	

[1]product-specific guidance (PSG)

Example: Acyclovir Ophthalmic Ointment

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Acyclovir

August 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic acyclovir.

Active Ingredient:	Acyclovir
Dosage Form; Route:	Ointment; ophthalmic
Strength:	3%
Recommended Study:	In vitro option

In vitro option

The proposed test drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD). Bioequivalence may be established based on comparative in vitro testing of three exhibit batches of both the test product and designated Reference Standard (RS) product include:[3]

- Appearance.
- Polymorphic form of acyclovir.
- Acidity and alkalinity of the extracted ointment base.
- Rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates.
- Drug particle size and size distribution.
- In vitro drug release tests of acyclovir from the test and RS products. Detailed information on development and validation of a proposed in vitro drug release testing method should be provided.

Unique Agency Identifier: PSG_202408

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

IVRT for BE Purpose
Example Complex Injectables

Route; dosage form	Active ingredient	Uses of IVRT
Intravenous; solution	• Meloxicam	In vitro only BE option is available in these PSGs; IVRT is used as part of the in vitro only BE approach; The IVRT is to show comparable rapid release between the test and reference products
Intravenous; for suspension	• Dantrolene sodium	
Intravenous, subcutaneous; powder	• Azacitidine	
Injection; injectable	• Verteporfin	
Injection; injectable	• Methylprednisolone acetate • Penicillin G benzathine • Triamcinolone acetonide	In vitro only BE option is available in these PSGs; IVRT is used as part of the in vitro only BE approach
Subcutaneous; powder	• Degarelix acetate	
Subcutaneous; injection	• Lanreotide	
Intravenous; emulsion	• Clevidipine	
Infiltration; solution, extended release	• Bupivacaine	

IVRT for BE Purpose
Example Complex Injectables (Cont.)

Route; dosage form	Active ingredient	Uses of IVRT
Injection; injectable, liposome	• Amphotericin B • Daunorubicin citrate • Doxorubicin hydrochloride	In vitro leakage rates as part of liposome characteristics is used in conjunction to an in vivo study with pharmacokinetic (PK) endpoints
Intravenous; injectable, liposome	• Irinotecan	
Injection; injectable liposomal	• Bupivacaine	
Intravenous; powder (albumin-bound nanoparticles)	• Paclitaxel	In vitro release kinetics as part of in vitro characteristics is in conjunction to an in vivo study with PK endpoints
Intramuscular; injectable (polymeric microspheres)	• Risperidone	IVRT is used in conjunction to an in vivo study with PK endpoints

IVRT for BE Purpose
Example Complex Inserted Products

Route; dosage form	Active ingredient	Uses of IVRT
Intrauterine; Intrauterine device	Levonorgestrel	IVRT throughout the intended period of product use (5 years) is used in conjunction to an in vivo/ex vivo study
Vaginal; extended-release insert	Estradiol	IVRT is used in conjunction to an in vivo study with PK endpoints
Vaginal; system	Progesterone	
Intrauterine; Intrauterine device	Copper	In vitro cupric ion release testing is used in conjunction to a comparative clinical endpoints BE study

Example: levonorgestrel intrauterine device

Contains Nonbinding Recommendations

Draft Guidance on Levonorgestrel

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Levonorgestrel

Dosage Form; Route: Intrauterine Device; intrauterine

Strength: 52 mg

Recommended Studies: Two studies: in vitro and in vivo/ex vivo

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

- Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
- Equivalent physicochemical and mechanical characteristics including 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) Degree of crosslinking of poly(dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane; 3) Mechanical properties of the drug reservoir and the drug rate controlling membrane; 4) Appearance, memory, mechanical properties of the T-body; and 5) Breaking force of the removal thread comparable to the Reference Standard (RS).
- Same dimensions with respect to each component as the RS.

A. Comparative in vitro drug release

Acceptable comparative in vitro drug release of levonorgestrel from the test and RS products throughout the intended period of product use (5 years). Any accelerated dissolution method that correlates to the real-time drug release behavior may be submitted for the Agency's consideration through either a controlled correspondence or as part of a pre-ANDA meeting request.

B. In vivo/ex vivo clinical study

Type of study: In vivo/ex vivo study of residual levonorgestrel and serum levonorgestrel
Design: One year, single-dose, randomized, parallel in vivo study
Strength: 52 mg
Subjects: Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive. The enrolled population should include a sufficient number of nulliparous women.
Prerequisite: Twelve months of in vitro levonorgestrel drug release data demonstrating comparable release profiles for the test product and the RS product should be available prior to placing the test product in study subject.

Analytes to measure:

BE for Additional Strengths

- Additional strengths of modified-release products may be demonstrated to be bioequivalent to the corresponding reference product strengths under 21 CFR 320.24(b)(6) if all the following conditions have been met[1]:
  - The reference product demonstrates dosage form equivalence among different strengths and demonstrates similar dissolution performance across different strengths
  - The test product includes the same excipients for different strengths and the ratios of drug and excipients among different strengths of the test product is justified and appropriate for the drug release mechanism of the test product (e.g., drug and excipients of different strengths can be either proportional or not proportional in quantity).
  - The additional strength of the test product has the same drug release mechanism as the strength of the test product that underwent an acceptable in vivo BE study compared to the reference product.
  - Dissolution testing of all strengths is acceptable. The drug products should exhibit similar dissolution profiles between the strength on which the BE testing was conducted and other strengths, based on the similarity factor (f2) test or other appropriate statistical approaches (e.g., a multivariate model independent approach or a model dependent approach) in at least three dissolution media (e.g., a pH of 1.2, 4.5, and 6.8).

[1] *Bioequivalence Studies With Pharmacokinetic Endpoints for Drug Submitted Under an ANDA* - Guidance for Industry (August 2021)

Example: IVRT to support waiver request of in vivo testing for additional strengths

Per PSG on Paliperidone palmitate extended-release injectable, waiver request of in vivo testing for 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, and 234 mg/1.5 mL (if not studied in vivo) can be based on:

- acceptable BE study on the 156 mg/mL strength,
- acceptable in vitro dissolution testing of all strengths
- proportional similarity of the formulations across all strengths

In this case, the f2 values comparing the additional strengths of the test product to the bio-study strength of the test product should be ≥50 in the recommended dissolution media.

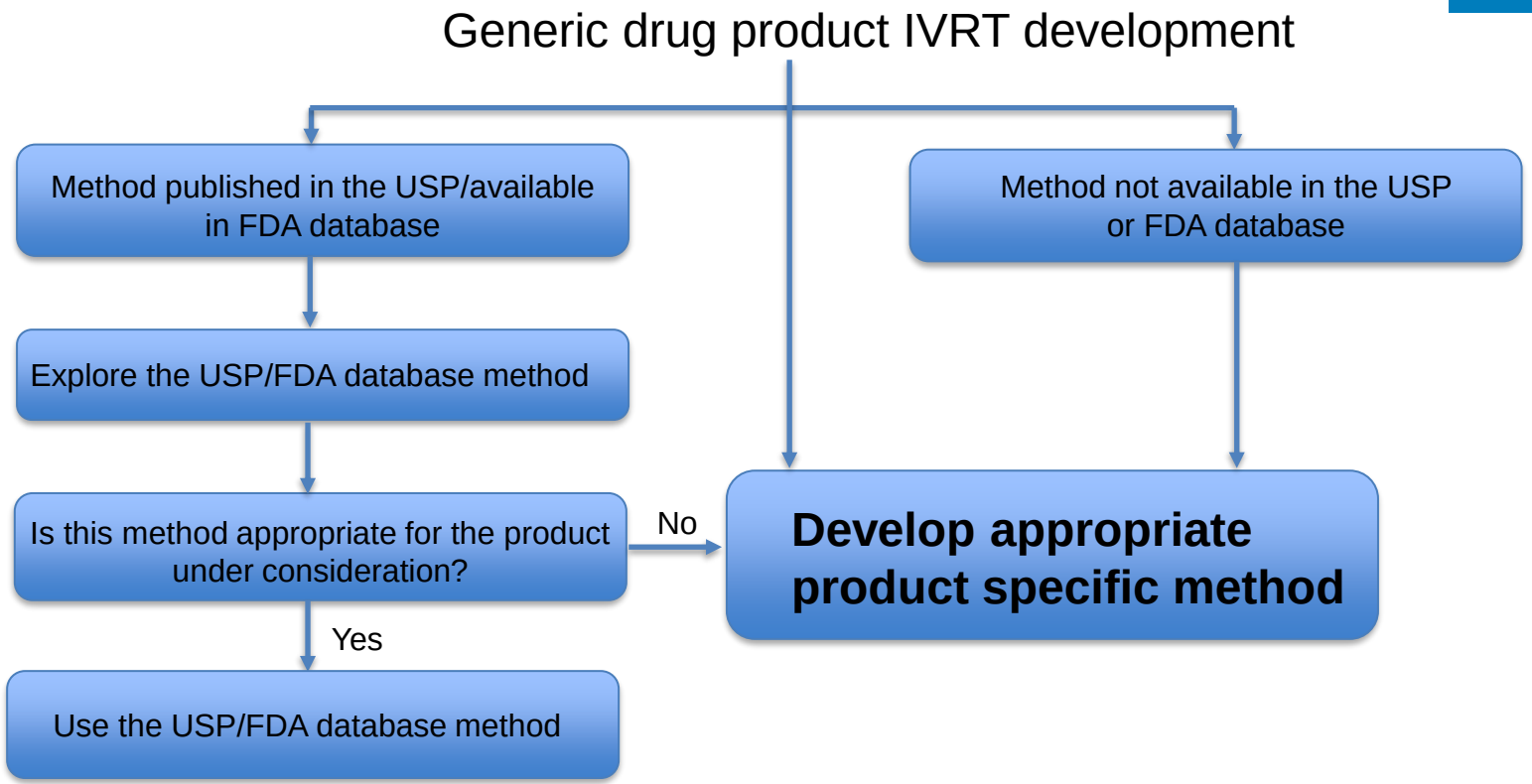
Considerations of IVRT for BE purpose

- IVRT is a component of the in vitro testing that may support BE determination and as such the developed IVRT method should be able to discriminate batches of product that are intentionally made to be not bioequivalent, i.e., manufactured with meaningful and intentional variations in critical quality attributes (CQA) of the drug product.
- When IVRT is used as part of a totality of evidence approach, in general, it is not expected/required to correlate with or be predictive of in vivo bioavailability.
- For products intended for rapid dissolution after injection, such as dantrolene, the IVRT is aimed to show comparative fast release. Discriminative power may not be practical for this type of product.

IVRT for QC purpose

- IVRT is an important quality control tool used for monitoring drug stability and consistency of manufacturing process.
  - Detect variation due to product manufacturing
  - Detect changes during product storage that may negatively impact product performance
  - Support minor/moderate CMC changes

Approaches to Develop an IVRT



Courtesy of Vidula Kolhatkar, considerations on in vitro drug release testing for long-acting drug products for quality control, SBIA 2019

IVRT Acceptance Criteria

- The complete in vitro drug-release profile data (n = 12) from BE (clinical or in vitro) and registration/stability batches should be used for setting the in vitro drug-release acceptance criteria.
- A minimum of three time points may be used to set the acceptance criteria (i.e., sampling time points and acceptance limits) for extended drug-release products from the lots used in the clinical trials and primary stability batches.
- These time points should cover the early, middle, and late stages of the drug-release profile. The last time point should be where at least 80% of the 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 drug-release profile has been reached.
- In general, the selection of the drug release acceptance criteria ranges is based on mean target value ±10% and > 80% for the last sampling time point. Wider criteria range may be acceptable if they are supported by an approved in vitro-in vivo correlation or physiologically based PK model.

General Information for IVRT Establishment

- Should submit an in vitro drug release method development report and validation report supporting the selection of proposed IVRT method. These reports should contain information on:
  - drug substance solubility data over the physiologic pH range
  - detailed description of the IVRT method, along with the developmental parameters supporting the selection of the proposed method as the optimal test
  - complete dissolution data (e.g., number of dosage units, mean, SD, %CV at each time point and mean profiles)
  - data (individual dissolution data and mean dissolution profiles) to support the discriminating ability of the selected method
  - supportive validation data for the dissolution method including the analytical method for assaying samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc.)

In Vitro-In Vivo Correlation (IVIVC)

- Another regulatory application of IVRT is its use for establishing an IVIVC
- Although FDA's published Guidance for Industry - *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997) is for ER oral dosage form, the framework and general principle of this guidance may be applicable to IVIVC development of other products.
- IVIVC may be used to
  - set dissolution specifications
  - serve as surrogate for an in vivo BE when it is necessary to document BE during the initial approval process or because of certain pre-or post approval changes

IVIVC (Cont.)

- For the generic drug development, an IVIVC may be used to support the use of IVRT as a surrogate for the in vivo BE study. However, for non-oral complex drug products, it is generally challenging to establish an IVIVC. Developing an IVIVC may not be easier than conducting an in vivo BE study.
- IVIVC may be used to support an in vitro alterative BE approach. In such case, an IVIVC can be used to identify the CQA design space. Level C IVIVC may be acceptable.

Summary

- IVRT is a useful tool to support regulatory approval of complex generic ophthalmic, injectable, implantable, and inserted products, for BE and QC perspectives.
- Applicants should submit sufficient information to support that an IVRT method is appropriate for its intended purpose, e.g., drug substance solubility, data to support the selection of the proposed method as the optimal test and data to support discriminative ability of the selected method.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