Expectations and Common Deficiencies for IVRT Studies Submitted in ANDAs for Ophthalmic Emulsion Products

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Disclaimer:

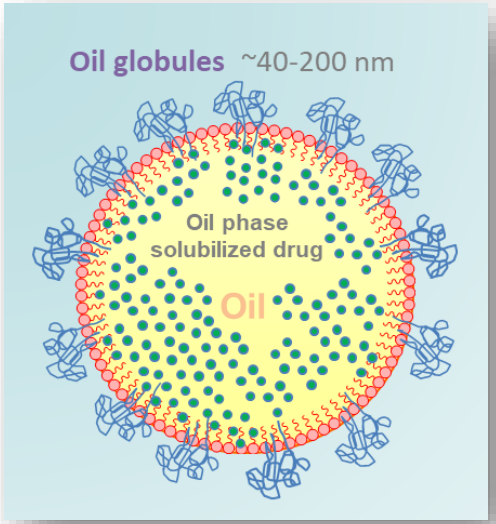
The current presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outlines

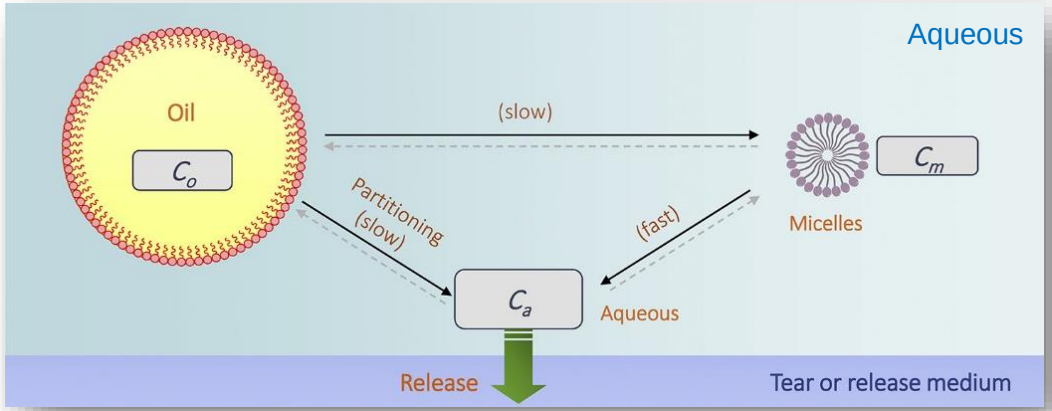
- Overview of ophthalmic emulsions
- Role of IVRT in bioequivalence (BE) demonstration for ophthalmic emulsion drug products
- Purpose of IVRT studies for ophthalmic emulsion drug products
- Overview and general expectations for high quality submissions of IVRT studies
- BE assessment of IVRT studies for ophthalmic emulsion products
- Common deficiencies observed during BE assessment of IVRT studies
- Take Home Message

Ophthalmic Emulsions – A Quick Overview

- Topical, locally-acting, ophthalmic formulation.
- Complex formulation containing active ingredient solubilized in oil droplets and dispersed in aqueous phase.



Adapted from an internal 2019 FDA presentation by Darby Kozak, Office of Research and Standards (ORS)



Dong, Y. et al. (2020) Evaluating drug distribution and release in ophthalmic emulsions: Impact of release condition

Purpose of IVRT Studies for Ophthalmic Emulsion Drug Products

- To support BE as part of a battery of in vitro tests by demonstrating that two products with similar formulations have a comparable drug release rate.
- Reflects the combined effect of the physical and chemical properties of the active ingredient, the drug product formulation, as well as manufacturing process on product performance.
- Does not need to mimic the in vivo conditions/performance or predict the therapeutic effect of the drug.

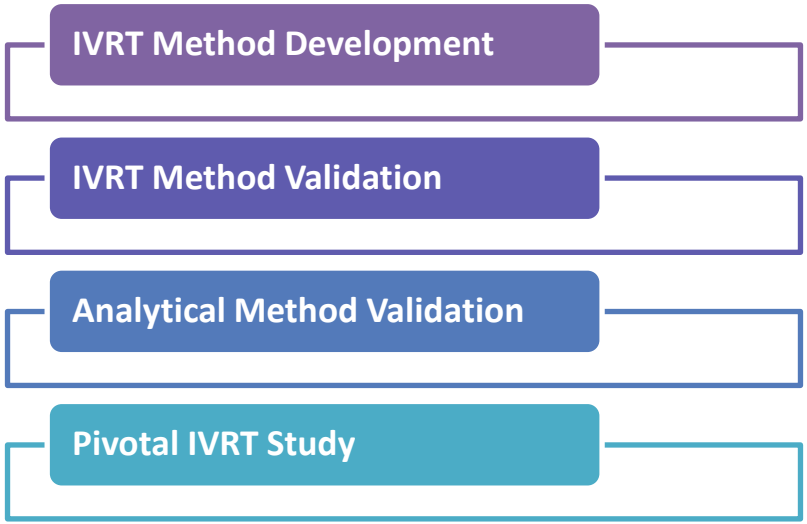
IVRT in Support of BE Demonstration for Ophthalmic Emulsion Drug Products

- Ophthalmic emulsion drug products: Cyclosporine Ophthalmic Emulsion, 0.05% and Difluprednate Ophthalmic Emulsion, 0.05%
- Product-specific guidance (PSG) recommendations for demonstrating BE using in vitro option:
  - ✓ The test and reference formulations should be qualitatively (Q1) and quantitatively (Q2) the same.
  - ✓ Acceptable comparative physicochemical characterizations of the test and reference formulations.
  - ✓ **Acceptable comparative in vitro drug release rate of the active ingredient from the test and reference formulations**. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

Overview of IVRT Study Submissions

- Increasing trend of ophthalmic emulsion and topical product submissions containing IVRT studies in recent years.
- However, there are challenges for IVRT studies submitted in support of BE due to:
  - lack of compendial IVRT methods and
  - no specific USP apparatus designed to conduct IVRT for ophthalmic emulsion products.
- Many IVRT deficiencies are related to incomplete submissions.
- BE deficiencies related to IVRT studies are often classified as major.

General Expectations Regarding IVRT Study Submissions



- Separate reports for method development, IVRT method validation, analytical method validation, and pivotal study are preferred.
- Provide step-by-step details of test procedures so that assessors are able to evaluate the appropriateness of IVRT study conduct.
- Provide all necessary data and calculations so that assessors are able to verify the results.

Location of IVRT Study Information in the ANDA Submission

- **Module 2.7.1:**
  - BE summary tables
- **Module 5.3.1:**
  - Study reports:
    - ❑ Method development
    - ❑ IVRT method validation
    - ❑ Analytical method validation
    - ❑ Pivotal IVRT study
  - Study protocols and standard operating procedures (SOPs) that were effective at the time of study.
  - 100% complete numerical raw data and chromatograms.
  - All original, re-injected, repeated and re-integrated analytical runs.
  - Individual concentration datasets used to calculate drug release rate for the test and reference formulations in SAS .xpt format.

BE Assessment of IVRT Studies

OGD evaluates the following non-exhaustive list of data/information to determine the acceptability of IVRT studies submitted in an ANDA:

- **IVRT Study Information**
  - Study number, site, and address
  - IVRT experiment dates and sample analysis dates
  - IVRT method description (apparatus, medium, dose amount, dosing application, membrane, receptor solution, stirring rate,… etc.)
  - Analytical method description (instrument, mobile phase, buffers, diluent, chromatographic conditions).
  - Test and reference lots used (lot number, manufacturing and expiration dates, potency, batch size,… etc.)

BE Assessment of IVRT Studies

- **IVRT Method Development:**
  - Detailed documentation on how IVRT method was optimized/developed.

    ❑ Parameters: sample loading volume, selection of sampling time points, equipment/apparatus, media, receptor solution, membrane, temperature, agitation/rotation speed, pH, sink conditions, surfactant type and concentrations,… etc.

    ❑ Information on how the IVRT method can capture the differences in drug release resulting from differences in formulation and manufacturing conditions.

    ❑ Demonstration that the method parameters selected for the IVRT are appropriate and necessary.

BE Assessment of IVRT Studies

- **IVRT Method Validation**
  - Method precision (repeatability)
  - Intermediate precision
  - Robustness (changes in temperature, pH of the drug release medium, dose, stirring rate,… etc.)
  - Membrane inertness
  - Solution stability
  - Recovery
  - Mass balance
  - Discriminatory ability (Sensitivity, Specificity, and Selectivity)

- **Analytical Method Validation**
  - Linearity and Range
  - Recovery
  - Intra- and inter-day precision and accuracy
  - Selectivity
  - Specificity
  - Dilution Integrity
  - Filter validation
  - Solution Stability

Common Deficiencies Observed During BE Assessment of IVRT Studies for Ophthalmic Emulsion Products

Insufficient details on apparatus validation; experimental set-up; method controls

Missing information/insufficient data for validation of method parameters

Inability/inadequate data showing discriminatory ability of method

Insufficient information on data analysis/data presentation

Inadequate documentation, organization and submission of IVRT reports

Individual reports not submitted for method development and validation

Missing information on mass balance for IVRT methods that use diffusion membrane

Lack of submission of raw data (.xpt files, chromatograms, related SOPs/Protocols)

Commonly Missing Study Information/Justification

- Information on IVRT apparatus and/or analytical instrument
- Dose
- Membrane type and pore size
- Stirring/agitation rate
- Sampling schedule, duration, and volume
- Study dates (IVRT experiment and sample analysis)
- Identity of the lots used during pivotal IVRT study as well as during IVRT method development and validation
- Missing detailed IVRT procedure, e.g., whether the membrane was pre-soaked or not and for how long, if the pH of the medium was kept constant for the duration of the IVRT study.

Other Common Deficiencies for IVRT Studies

- Inconsistent information throughout the submission.
- Incomplete data for studies involving multiple replicates;
  - Number of replicates unclear.
  - Only summary statistics are provided but not individual data for each replicate tested.

Inadequate/Insufficient Data on IVRT Method Development and Validation

- Missing protocols and/or standard operating procedures (SOPs) that were effective at the time of the IVRT method development and validation.
- Lack of data/justification to support optimization of the IVRT method.
- Missing apparatus qualification information demonstrating the reproducibility and robustness of the IVRT method.
- Missing mass balance data to support that the IVRT method measures drug release from the formulation rather than the transfer of formulation/oil droplets across membrane.
- Missing/inadequate data showing the discriminatory ability of the IVRT method in terms of sensitivity, selectivity, and specificity. In particular, missing information, explanation, and experimental data demonstrating the ability of the IVRT method to discriminate the effect of process variability in the production of the test formulation.

Inadequate/Insufficient Data on the Analytical Method Validation

- Missing protocols and/or SOPs that were effective at the time of the analytical method validation.
- Missing/inadequate information on IVRT sample processing prior to analysis (e.g., dilution procedure, data on dilution integrity,… etc.)
- Missing information on the maximum storage period (if applicable) and storage condition (i.e., temperature) for the IVRT samples.

Take Home Message

- The number of ANDA submissions containing IVRT studies has increased in recent years.
- IVRT is a tool to ensure consistent performance and quality of generic products and provide an effective approach to monitor post-approval changes, scale-up, lot-to-lot changes and stability studies for ophthalmic emulsions.
- BE-related IVRT deficiencies are often classified as major.
- Lack of standardized methods and tools for measuring in vitro drug release is a challenge for the Agency and for industry.
- Many of the deficiencies presented may be avoided by:
  - Providing detailed data and rationale to support the selection of IVRT method.
  - Providing complete and detailed information to allow for proper assessment of the appropriateness of IVRT study conduct and the accuracy of the results provided.

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Thank you