Contains Nonbinding Recommendations

Draft Guidance on Silver Sulfadiazine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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: Silver sulfadiazine

Dosage Form; Route: Cream; topical

Recommended studies: In vitro study

To qualify for the in vitro approach to demonstrate bioequivalence for silver sulfadiazine topical cream 1% the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products should be pharmaceutically equivalent as defined in the Agency publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) and should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*.[1] To demonstrate acceptable Q1 and Q2 sameness of the test product with respect to the RLD product, the test product should contain the same inactive ingredients in the same quantitative composition (±5% of the RLD concentration of that inactive ingredient), and no concentration of any inactive ingredient should exceed the allowed limit listed in the inactive ingredient database for the applicable route of administration.

B. The test and RLD products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product, including the following characterizations for each lot:

    1. Assessment of appearance
    2. Analysis of the silver sulfadiazine polymorphic form in the drug product
    3. Analysis of globule and/or particle size distribution and crystal habit with representative microscopic images at multiple magnifications
    4. Analysis of the rheological behavior, which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

a. A complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified.
b. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
c. The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

5. Analysis of specific gravity and pH of the cream, as well as any other potentially relevant physical and structural similarity characterizations.

C. The test and RLD products should have an equivalent rate of silver sulfadiazine release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method performed in a manner compatible with the general procedures and statistical analysis method specified in the United States Pharmacopeia (USP) General Chapter <1724>, Semisolid Drug Products – Performance Tests. The cumulative amount of silver sulfadiazine released at each sampling time point should be reported for each diffusion cell, as well as relevant summary statistics for the IVRT study. Detailed study protocols and reports should be submitted in module 5.3.1 of the electronic Common Technical Document (Reports of biopharmaceutic studies) including experimental procedures, study controls, quality management procedures, and data analyses.

Additional comments:

1. The Office of Generic Drugs (OGD) recommends that the lots of test and RLD products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared. The influence of any differences in the container closure systems between the test and RLD products, which may influence the physicochemical properties of the cream when dispensed, should be considered in the design of the physical and structural characterization studies and discussed in the associated reports.

2. Investigators should perform the physical and structural characterization studies within a quality management system that is compatible with applicable principles of Good Laboratory Practices (GLP) described in 21 CFR 58. Any aspects of the quality management system that are not compatible with these GLP principles, and any aspects of GLP that are not applicable, should be identified in the relevant physical and structural characterization study protocols and final reports. Experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol deviations, should be reported.

3. In addition, investigators should perform the IVRT validation and pivotal studies within a quality management system that is compatible with applicable principles of GLP described in 21 CFR 58. Any aspects of the quality management system that are not

compatible with these GLP principles, and any aspects of GLP that are not applicable, should be identified in the relevant IVRT study protocol and final report.

4. **IVRT Method Development:** The results of relevant IVRT method development studies should be submitted for review, although such exploratory studies may not be performed using validated test method or sample analytical procedures, or within a quality management system that is compatible with applicable GLP principles:

    a. **Method Parameters:** Information should be provided to support the selection of the IVRT apparatus, product dose amount, sampling times, stirring/agitation rate, and other parameters of the test method.

    b. **Membrane:** Information on silver sulfadiazine membrane binding and chemical compatibility with relevant receptor solutions should be provided to support the inertness of the membrane selected, and information on the linearity and precision of the resulting silver sulfadiazine release rate in an IVRT should be provided to support the selection of a membrane for the test method.

    c. **Receptor Solution:** Information on the empirical solubility and stability of silver sulfadiazine in the receptor solution, as well as information on the linearity and precision of the resulting silver sulfadiazine release rate in an IVRT should be provided to support the selection of a receptor solution for the test method.

5. **IVRT Method Validation:** The apparatus, methodologies, and study conditions utilized in the IVRT pivotal study should be appropriately validated, qualified, verified, and/or justified. Detailed protocols and well-controlled study procedures are recommended to ensure the precise control of dosing, sampling, and other IVRT study variables or potential sources of experimental bias. The validation of the IVRT method should incorporate the following qualifications and controls, performed using validated sample analytical procedures, as applicable:

    a. **IVRT Apparatus Qualification:** Suitable apparatus for the IVRT method are described in USP General Chapter <1724>. These include different models of a vertical diffusion cell, an immersion cell, and a flow through cell used with USP Apparatus 4. The operating principles and specific test procedures differ among the various apparatus; relevant procedures for installation, operational and performance qualification available from the manufacturer may be utilized. The laboratory qualification of each diffusion cell should, at minimum, qualify the diffusional area of the orifice in which the membrane is mounted, the volume of the receptor solution compartment in each diffusion cell, the control of a 32°C ± 1°C temperature (at the membrane), and the control of the rate of stirring or agitation, as applicable.

    b. **IVRT Membrane Qualification:** Membrane inertness may be evaluated in relation to membrane binding of silver sulfadiazine in the receptor solution (at a concentration relevant to the average concentration of silver sulfadiazine in the receptor solution at the end of the test). Determinations may be based upon 3 replicate membrane

incubations for the IVRT duration (e.g. 6 hours) at 32°C ± 1°C. Three replicate control incubations may be performed in parallel, without membranes, to monitor for silver sulfadiazine loss that is not associated with membrane binding. Aliquots of these solutions may be collected before and after the duration of incubation, to assess any decrease in the amount of silver sulfadiazine in solution. The recovery of silver sulfadiazine in solution is recommended to be within the range of 100% ± 5% at the end of the test duration to qualify the inertness of the membrane.

c. **IVRT Receptor Solution Qualification:** The composition of the receptor solution utilized for the IVRT study should be justified and the minimum solubility of silver sulfadiazine in the IVRT receptor solution should be empirically determined in triplicate with silver sulfadiazine dissolved to saturation in the receptor solution, to a concentration exceeding the highest sample concentration obtained in the pivotal IVRT study, ideally by an order of magnitude or demonstrably sufficient to facilitate the linearity of the release rate for the duration of the study.

d. **IVRT Receptor Solution Sampling Qualification:** The accuracy and precision of receptor solution sample collection at each time point should be appropriately qualified.

e. **IVRT Receptor Solution Sample Analytical Method Validation:** The receptor sample HPLC analysis procedures should be validated in a manner compatible with the current FDA Guidance for Industry on Bioanalytical Method Validation, and/or the ICH Harmonised Tripartite Guideline on Validation of Analytical Procedures Q2 (R1). The validation of the receptor sample analytical method should include relevant qualifications of dilution integrity as well as stability assessments with the highest relevant temperature in the receptor solution, which may be warmer than 32°C, for the duration of the IVRT study (e.g., 34°C for 6 hours).

f. **IVRT Environmental Control:** Ambient laboratory temperature and humidity during the study should be monitored and reported. An environmentally controlled temperature range of 21°C ± 2°C and a humidity range of 50% ± 20% relative humidity are recommended.

g. **IVRT Linearity and Range:** The linearity (r2 value) of the release rate (slope) may be calculated across the range of the sampling times, which corresponds to the IVRT study duration. Linearity may be compared within and across all IVRT runs, and a minimum r2 value ≥ 0.90 across the IVRT study duration (time range) is recommended.

h. **IVRT Precision and Reproducibility:** The intra-run and inter-run precision and reproducibility may be compared for the release rate (slopes) calculated for each diffusion cell. The mean, standard deviation, and percent coefficient of variation (%CV) among slopes may be calculated within and across all runs, and a minimum intra-run and inter-run %CV $\leq$ 15% is recommended. Runs may be organized to

facilitate a simultaneous evaluation of intra/inter-instrumentation and/or intra/inter-operator precision and reproducibility.

i. **IVRT Recovery, Mass Balance & Dose Depletion:** The recovery of released silver sulfadiazine in the receptor solution may be characterized in each diffusion cell as the accumulated amount of silver sulfadiazine in the receptor solution over the IVRT duration. This may be expressed as a percentage of the amount of silver sulfadiazine in the applied dose. The average dose depletion may thereby be estimated and should be reported.

j. **IVRT Discrimination Sensitivity, Specificity and Selectivity:** The IVRT method should be able to discriminate silver sulfadiazine release rates from similar formulations. This may be evaluated by comparing the release rate from the silver sulfadiazine cream 5% with that from two comparable formulations in which the concentration of silver sulfadiazine has been altered – one with a higher strength (e.g., 7.5%) and one with a lower strength (e.g., 2.5%). The composition and procedures for preparation of these reference and test formulations should be reported, although these formulations may not be prepared in a manner compatible with current Good Manufacturing Practices. The discrimination ability of the IVRT method may be described using three concepts of discrimination ability: sensitivity, specificity, and selectivity.

   i. IVRT Sensitivity is the ability to detect changes in the release rate, as a function of silver sulfadiazine concentration in the formulation. If the IVRT method consistently identifies higher or lower rates of release for test formulations with increased or decreased silver sulfadiazine concentrations, respectively, relative to the reference formulation run in parallel on the same day, the IVRT method may be considered sensitive.

   ii. IVRT Specificity is the ability to accurately monitor the proportionality of changes in the release rate as a function of drug concentration in the formulation. This proportionality may be illustrated in a plot of the relationship between the formulation concentration and the average IVRT release rate (slope). Specificity may be quantified and reported as the linearity (ideally a minimum r2 value of $\geq$ 0.90) of the correlation of formulation concentration to average IVRT release rate (slope).

   iii. IVRT Selectivity is the ability of the IVRT method to be sufficiently selective to identify that the different silver sulfadiazine release rates from the altered concentration test formulations are inequivalent with respect to the silver sulfadiazine release rate from the reference product. To support supplemental selectivity, other test formulation alterations may involve changes in inactive ingredients, changes in inactive ingredient concentration(s), or altered manufacturing processes. Determination of (in)equivalence in release rates may be evaluated using the statistical approach described in USP <1724>.

k. **IVRT Robustness:** The IVRT method may be considered robust to a variation in the test method if the average slope of that IVRT run (under altered conditions) is within ± 15% of the average slope of the Precision & Reproducibility IVRT runs. Robustness testing may encompass variations in the IVRT method that are relevant to the apparatus and test method, for example:

   i. Temperature variations (e.g. - 1°C and +1°C relative to 32°C ± 1°C)
   ii. Dose volume variations (e.g. +10% and -10% in the dose volume)
   iii. Receptor solution variations (e.g. change in composition and/or pH)
   iv. Mixing rate variation (e.g. differences in stirring speed, or without stirring)

6. Retention samples should be randomly selected from the drug supplies received prior to dispensing during the pivotal IVRT study in which the test and RLD products are compared. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding considerations for retention of study drug samples and to 21 CFR 320.36 for requirements for maintenance of records of BE testing.

7. For the IVRT pivotal study, a detailed description of the blinding procedure should be provided in the study protocol and final report. The packaging of the test and RLD products should be similar in appearance to maintain adequate blinding of the investigator and any experimental operators.

8. In the IVRT pivotal study, the test and RLD products should be dosed in an alternating sequence on successive diffusion cells; it is possible to assign two possible sequences (illustrated below) one of which is randomly selected for dosing:
   a. ABABAB…
   b. BABABA…

9. Experimental observations that may have the potential to influence the interpretation of any study results should be reported, as well as any protocol deviations.