

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

- A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*, Revision 1 (May 2015).¹
- B. The test and RLD products are 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.
- C. The test and RLD products have an equivalent rate of acyclovir 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.
- D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments: Specific recommendations are provided below.

¹ Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*, Revision 1 (May 2015)

II. In vivo option:

Type of study: BE study with a clinical endpoint

Design: Randomized, double blind, parallel, three-arm, placebo-controlled, in vivo study

Strength: 5%

Subjects: Healthy, immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (cold sores)

Additional comments: Specific recommendations are provided below. Due to the modest efficacy demonstrated by the RLD, it is anticipated that a relatively large number of subjects would need to be enrolled.

Analytes to measure: Acyclovir (in vitro option only; see additional comments)

Bioequivalence based on (90% CI): See additional comments for the in vitro or in vivo option

Dissolution test method and sampling times: N/A

I. Additional comments relating to the in vitro option

A. Q1/Q2 Comparison

1. The test product should be pharmaceutically equivalent to the RLD product as defined in the Agency publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book).
2. 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 ($\pm 5\%$ 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. Physical and Structural Comparison

1. The Office of Generic Drugs (OGD) recommends that the lots of test and RLD products evaluated in the IVRT study should be the same as those evaluated in the IVPT study, and that these lots 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 are recommended to 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. Comparison of physical and structural similarity for the test and RLD products should include the following physicochemical characterizations for each lot of test and RLD products:
 - a. Assessment of appearance
 - b. Analysis of the acyclovir polymorphic form in the drug product
 - c. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications.
 - d. 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:
 - 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.
 - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
 - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.
 - e. Analysis of specific gravity, water activity, pH and any other potentially relevant physical and structural similarity characterizations.

C. IVRT Comparison

1. The IVRT pivotal study comparing the acyclovir release rates between the test and RLD products should be 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 acyclovir 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 biopharmaceutical studies) including experimental procedures, study controls, quality management procedures, and data analyses.

2. 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. In addition, investigators are recommended to 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. Retention samples should be randomly selected from the drug supplies received prior to dispensing during the IVRT study in which the test and RLD products are compared. 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. 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.
4. 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...
5. **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 acyclovir 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 acyclovir 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 acyclovir in the receptor solution, as well as information on the linearity and precision of the resulting acyclovir release rate in an IVRT should be provided to support the selection of a receptor solution for the test method.
6. **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 $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$ 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 the acyclovir in the receptor solution (at a concentration relevant to the average concentration of acyclovir 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 $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$. Three replicate control incubations may be performed in parallel, without membranes, to monitor for acyclovir 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 acyclovir in solution. The recovery of acyclovir in solution is recommended to be within the range of $100\% \pm 5\%$ 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 acyclovir in the IVRT receptor solution should be empirically determined in triplicate with acyclovir 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 (r^2 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 r^2 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 acyclovir in the receptor solution may be characterized in each diffusion cell as the accumulated amount of acyclovir in the receptor solution over the IVRT duration. This may be expressed as a percentage of the amount of acyclovir 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 acyclovir release rates from similar formulations. This may be evaluated by comparing the release rate from the acyclovir cream 5% with that from two comparable formulations in which the concentration of acyclovir 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 acyclovir concentration in the formulation. If the IVRT method consistently identifies higher or lower rates of release for test formulations with increased or decreased acyclovir 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 r^2 value of ≥ 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 acyclovir release rates from the altered concentration test formulations are in-equivalent with respect the acyclovir 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 $\pm 15\%$ 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 $+1^\circ\text{C}$ relative to $32^\circ\text{C} \pm 1^\circ\text{C}$)
 - 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)

D. IVPT Comparison

1. The recommended IVPT pivotal study design is a parallel, single-dose, multiple-replicate per treatment group study comparing the cutaneous pharmacokinetics of acyclovir from the test product versus the RLD using excised human skin with a competent skin barrier mounted on a qualified diffusion cell system.

2. The IVPT pivotal study should utilize a balanced design directly comparing the test and RLD products on skin from the same set of donors, each with the same number of replicate skin sections per donor per treatment group (dosed with either test or RLD product). Skin sections (diffusion cells) that are discontinued from the study based upon criteria specified in the study protocol may be replaced with new skin sections from the same donor to ensure that the final data set contains a balanced number of replicate skin sections (diffusion cells) dosed in each treatment group (test or RLD product) across all donors in the study.
3. The IVPT pivotal study protocol should incorporate considerations relevant to BE studies in general. Detailed study protocols and reports should be submitted in module 5.3.1 of the electronic Common Technical Document (Reports of biopharmaceutical studies) including experimental procedures, study controls, quality management procedures, and data analyses.
4. 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. In addition, investigators are recommended to perform the IVPT 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 IVPT study protocol and final report. Retention samples should be randomly selected from the drug supplies received prior to dispensing during the IVPT study in which the test and RLD products are compared. Experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol deviations, should be reported.
5. 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. The method of randomization should be described in the protocol and the randomization schedule provided, preferably in a SAS data set in .xpt format (created using the SAS XPORT procedure). It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the test and RLD products dosed in the study. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each skin section.
6. In the IVPT pivotal study, the test and RLD products should be dosed in an alternating sequence on successive diffusion cells (skin sections) from each donor. One of two dosing sequences (illustrated below) may be randomly assigned for each donor:

- a. ABABAB...
 - b. BABABA...
7. A single, un-occluded dose in the range of 5-15 mg cream/cm² that is retained on the skin for the duration of the study is recommended. An alternative study design (e.g., where the dose is not retained on the skin for the entire duration of the study) should be appropriately justified with particular consideration for the discrimination sensitivity of the IVPT study.
8. It is the responsibility of the applicant to determine the number of donors required to adequately power the IVPT pivotal study, however, a minimum of 4 dosed replicates per donor per treatment group (RLD or test) is recommended.
9. **IVPT Method Development:** The results of relevant method development IVPT studies should be submitted for review, although such exploratory studies may not be performed using validated procedures or sample analytical methods, or within a quality management system that is compatible with applicable GLP principles.
- a. **IVPT Method Development Studies:** The selection of the dose amount utilized in the study, even if within the recommended range, should be justified for each IVPT system based upon studies performed during IVPT method development. Different dose amounts may be compared in parallel to evaluate the consistency with which the dose can be applied, the relative precision and magnitude of the flux results, the influence of dose on the time course and pharmacokinetic parameters of the flux profiles, and the approximate range of acyclovir concentrations in receptor solution samples at different time points.
- Studies performed during IVPT method development may also support the selection of an appropriate sampling schedule and duration for the IVPT pivotal study. The study duration should be sufficient to characterize the cutaneous pharmacokinetics of acyclovir, including a sufficiently complete flux profile to identify the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points. The sampling frequency should be selected to provide suitable resolution for the flux profile, and a minimum of 8 non-zero sampling time points is recommended across the study duration (e.g. 48 hours). Information should be provided to support the selection of the IVPT apparatus, product dose amount, sampling times, stirring/flow rate, and other parameters of the test method
10. **IVPT Method Validation:** The apparatus, methodologies and study conditions utilized in the IVPT 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 IVPT study variables or potential sources of experimental bias. The validation of the IVPT method should incorporate the following qualifications and controls:

- a. IVPT Apparatus Qualification:** Suitable apparatus for the IVPT method include vertical diffusion cells and flow through diffusion cells. 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 skin is mounted, the volume of the receptor solution compartment in each diffusion cell, the control of a $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$ temperature (at the skin surface), and the control of the rate of stirring or flow rate, as applicable. The test system should control the diffusion cell thermoregulation so that the skin surface temperature is verified to be stable at $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for each diffusion cell prior to dosing (e.g., measured by a calibrated infrared thermometer), and monitored periodically throughout the duration of the experiment by measuring the temperature of a non-dosed control diffusion cell that is run in parallel with the other replicate dosed diffusion cells and connected to the same water bath or thermoregulation system.
- b. IVPT Membrane (Skin) Qualification:** Excised human skin is recommended as the membrane for the IVPT study. The validity of each skin section dosed in the study should be qualified using an appropriate test procedure to evaluate the stratum corneum barrier integrity. Acceptable barrier integrity tests may be based upon tritiated water permeation, trans-epidermal water loss (TEWL), or electrical impedance/conductance measured across the skin. The test parameters and acceptance criteria utilized for the skin barrier integrity test should be justified based upon relevant literature references or other information. The skin thickness should be measured and reported for each skin section and should be relatively consistent for all donors whose skin is included in the study, within limits specified in the study protocol. The assignment of replicate skin sections from a donor to each treatment group should be randomized, as feasible. It is acceptable to balance the distribution of skin thicknesses in each treatment group (test or RLD product) by a procedure specified in the study protocol.
- c. IVPT Receptor Solution Qualification:** The composition and pH of the receptor solution utilized for the IVPT study should be qualified in relation to its compatibility with the skin as well as the solubility and stability of acyclovir. The minimum solubility of acyclovir in the IVPT receptor solution should be empirically determined in triplicate with acyclovir dissolved to saturation in the receptor solution, to a concentration exceeding the highest sample concentration in the IVPT pivotal study, ideally by an order of magnitude. Strategies to improve the solubility of acyclovir in the receptor solution that may have the potential to alter the permeability of the skin are not recommended. The inclusion of an anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~0.01% gentamicin sulfate) is recommended to mitigate potential bacterial decomposition of the dermis and/or epidermis in the diffusion cell across the study

duration. The stability of acyclovir in the receptor solution samples should be validated as part of the receptor sample analytical method validation.

- d. **IVPT Receptor Solution Sampling Qualification:** The accuracy and precision of receptor solution sample collection at each time point should be appropriately qualified. For IVPT studies using a vertical diffusion cell, it is recommended that the entire receptor solution volume be removed and replaced at each time point to provide optimal solubility sink conditions. For IVPT studies using a flow-through diffusion cell, it may be necessary to qualify the lengths of tubing and associated dead volumes, to accurately calculate the lag time before a sample elutes through the tubing and is collected.
- e. **IVPT Receptor Solution Sample Analytical Method Validation:** The receptor sample analysis procedures should be validated in a manner compatible with the current FDA Guidance for Industry on Bioanalytical Method Validation. 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 IVPT study (e.g., 34°C for 48 hours) or for the longest interval between sampling time points for methods in which the entire receptor solution is replaced at each sampling time point. If the samples are processed in specific ways for analysis (e.g., by drying and reconstituting the receptor samples in a smaller volume to concentrate the sample and increase the effective analytical sensitivity, or by dilution of receptor solution samples into the validated curve range of the analytical method) those procedures should be validated (e.g., by qualifying the dilution integrity during the analytical method validation). The stability of acyclovir in the receptor solution sample should be validated in a receptor solution matrix that has been exposed to the underside of the skin in a diffusion cell under conditions relevant to the IVPT pivotal study.
- f. **IVPT 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. **IVPT Pilot Study:** Following the IVPT method development studies, a pilot IVPT study comparing the test and RLD products is recommended, to estimate the number of donors required for the IVPT pivotal study. A pilot IVPT study performed with multiple skin donors and a minimum of 4 replicate skin sections per donor per treatment group is recommended. As skin from an increasing number of donors is evaluated in the pilot study, the accuracy of the estimated number of donors needed to adequately power the IVPT pivotal study may improve. While skin from the same donors evaluated in the pilot study may also be utilized in the IVPT pivotal study, the results from the pilot study may not be combined with the results from the IVPT pivotal study for the purpose of

statistical analysis. In addition to the test and RLD products evaluated in the pilot study, a parallel assessment should be performed with a third product or formulation that is known or designed to be different from the RLD, to validate the selectivity of the IVPT method to discriminate differences in bioavailability.

- h. **IVPT Permeation Profile and Range:** The flux profile and cumulative permeation profile of acyclovir across the range of sampling times, which corresponds to the IVPT study duration, should be characterized based upon the results of the pilot IVPT study. The pilot study results should be plotted with error bars, comparing the permeation profiles for the three treatment groups in the pilot study, as separate plots for average flux and average cumulative permeation. The calculation of flux and cumulative total permeation is discussed in more detail below. The results of the pilot study should validate that the study duration (range) is sufficient to characterize the cutaneous pharmacokinetics of acyclovir, including a sufficiently complete flux profile to identify the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points. The results of the pilot study should also validate that the sampling frequency provides suitable resolution for the flux profile.
- i. **IVPT Precision and Reproducibility:** The pilot study flux and cumulative permeation results should be tabulated for each diffusion cell and time point, with summary statistics to describe the intra-donor average, standard deviation, and %CV among replicates as well as the inter-donor average, standard error, and %CV.
- j. **IVPT Recovery, Mass Balance & Dose Depletion:** The recovery of permeated acyclovir in the receptor solution may be characterized in each diffusion cell as the cumulative total permeation of acyclovir in the receptor solution over the IVPT duration. This may be expressed as a percentage of the amount of acyclovir in the applied dose. The minimum amount of dose depletion (not accounting for skin content) may thereby be estimated and should be reported.
- k. **IVPT Discrimination Sensitivity and Selectivity:** The discrimination ability of the IVPT method may be described using two concepts: sensitivity, and selectivity.
 - i. IVPT Sensitivity is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of acyclovir as a function of differences in acyclovir delivery. The IVPT method development study with different dose amounts may provide supportive evidence that the IVPT methodology is sensitive to differences in acyclovir delivery. Alternatively, studies with acyclovir formulations at higher and lower strengths relative to the RLD or that are otherwise rationally expected to increase and decrease drug delivery, or studies with different dose durations, if relevant to the IVPT study design, may support a demonstration of IVPT sensitivity. The differences in the IVPT cutaneous pharmacokinetic endpoints (discussed below) are not necessarily expected

to be specifically proportional to differences in the delivered dose. For example, three-fold differences in the dose (even if outside the recommended target dose range of 5-15 mg cream/cm²) may provide distinct flux curves, but may not result in three-fold differences in the cutaneous pharmacokinetic endpoints because the skin barrier may be rate limiting both in vitro and in vivo. If the IVPT method consistently demonstrates higher and lower flux profiles (and cutaneous pharmacokinetic endpoints) in response to increased and decreased dose amounts, respectively (or in response to other conditions expected to increase and decrease drug delivery, respectively) the IVPT method may be considered sensitive.

- ii. **IVPT Selectivity** is the ability of the IVPT method to discriminate that the cutaneous pharmacokinetics of acyclovir from a product or formulation that exhibits differences in acyclovir delivery is not equivalent to the cutaneous pharmacokinetics of acyclovir from the RLD product. The IVPT pilot study with the parallel assessment of the RLD product, the test product, and a third product or formulation that is known or designed to be different from the RLD may provide supportive evidence that the IVPT methodology is selective for differences in acyclovir delivery. The evaluation of (in)equivalence may be based upon the cutaneous pharmacokinetic endpoints and the statistical approach recommended below, although the sample size in the pilot study is not necessarily expected to adequately power the statistical analysis.

- I. IVPT Robustness:** A primary assumption related to robustness testing is that the test system performs consistently when all system variables (e.g., temperature, stirring rate) are at nominal settings. A value of robustness testing is that it can verify whether the system continues to provide a consistent output when specific variables are slightly varied, thereby qualifying operational ranges for those variables. However, the variability inherent in the permeability of human skin, whether in vitro or in vivo, may not be compatible with the primary assumption related to the consistency of the test system. Therefore, it may be challenging to qualify broad operational ranges, and study procedures should be controlled as precisely as possible (discussed in more detail below).

Relevant results from studies during IVPT method development that appear to support the robustness of the IVPT system may be reported and discussed. Similarly, any concerns that the permeability of acyclovir into and through human skin is robust to certain conditions that may be used to evaluate the discrimination sensitivity and/or selectivity of the IVPT method may be discussed in relation to specific results from the IVPT method development and/or pilot studies.

- m. IVPT Qualification and Control of Study Procedures:**

- i. Study procedures that have the potential to influence the results of the study should be appropriately justified, qualified, and/or controlled.

- ii. Control of procedures related to the skin include the consistent control across the study of the skin preparation (e.g., dermatoming of skin sections) and the thickness of skin sections mounted on diffusion cells, as well as the skin storage conditions, including the duration for which the skin was frozen and the number of freeze-thaw cycles to which the skin was exposed. Skin from the same anatomical location should be utilized from all donors, and the demographics (age, race, sex) should be reported for all donors.
- iii. Control of procedures related to the dose include the control of the area of dose application, the dose amount, the dosing technique, the dose duration, and the blinding and randomization procedures for dosing. The test and RLD products should be dosed in an identical and consistent manner for all diffusion cells in the study. Differences in dosing technique may have the potential to alter the metamorphosis of the dosage form on the skin and inconsistencies in the diameter of the area dosed on each diffusion cell may significantly influence the dosed area and contribute to errors in the calculation of flux.
- iv. Control of procedures related to sampling include the control of sampling time precision, the sampling technique, the duration of sampling and replacement of receptor solution, the sample volume or flow rate, and sample handling and storage.
- v. Control of procedures related to study should include a non-dosed control skin section from each skin donor, which should be mounted in a diffusion cell and otherwise treated identically to the dosed skin sections, including sampling of the receptor solution at all time points to ensure that acyclovir concentrations monitored in the receptor solution are associated with the dose applied in the IVPT pivotal study, and not acyclovir contamination in the skin from that donor that might permeate into the receptor solution across the duration of the study. A pre-dose “zero” sample collected from each diffusion cell is also recommended, which may identify potential contamination associated with each skin section and/or each diffusion cell.
- vi. The IVPT pivotal study design, methodology and diffusion cell apparatus considerations relating to sampling precision should be controlled as precisely as possible and justified. For example, it may be appropriate to stagger the dose application on successive diffusion cells and to synchronize the sampling time points with the dosing time for that diffusion cell, to ensure consistent durations between dosing and sampling of all diffusion cells.

11. IVPT pivotal Study Inclusion Criteria (the sponsor may add additional criteria)

- a. Healthy, normal, barrier-competent skin from male and/or female donors of at least 18 years of age. Inclusion criteria related to donor demographics (age, race, sex) should be

specified in the study protocol and demographic information should be reported for each donor.

- b. The skin may be harvested following excision from patients undergoing a surgical procedure or excised from cadavers. A consistent source is recommended for all the skin used. The anatomical region specified in the study protocol (e.g., posterior torso) should be consistent for all donors whose skin is included in the study.
- c. The study protocol should specify the inclusion (acceptance) criteria for skin sections based upon the barrier integrity test result, which should be reported for each skin section.
- d. The study protocol should specify and justify inclusion criteria related to the temperature and duration of skin storage as well as the number of freeze-thaw cycles, all of which should be reported for each donor's skin.
- e. The study protocol should specify and justify the inclusion criteria related to the skin harvesting/processing procedures and skin thickness (e.g., dermatomed skin of $500\mu\text{m} \pm 250\mu\text{m}$ thickness) utilized in the IVPT study.

12. IVPT pivotal Study Exclusion Criteria (the sponsor may add additional criteria)

- a. Skin with tattoos, stretch marks or any sign of dermatological abnormality should be excluded from the study.
- b. Skin exhibiting a significant density of terminal hair is not recommended and should be excluded from the study.
- c. While gentle washing or rinsing of the skin surface is appropriate, skin that has been subjected to shaving with a blade, abrasive polishing, tape-stripping, or cleansing with alcohols, solvents or other strong solutions that could damage the skin barrier is not recommended and should be excluded from the study.
- d. Skin from donors with significant background levels of acyclovir or other compounds that may interfere with the quantification of acyclovir in receptor solution samples should be excluded from the study.
- e. Skin from donors exhibiting a high barrier integrity test failure rate among replicate skin sections may be excluded from the study, and skin from an alternative donor may be utilized instead.

13. The cutaneous pharmacokinetic endpoints for the IVPT pivotal study are based upon parameters that characterize the rate and extent to which acyclovir permeates into and through the skin, and becomes available in the receptor solution. Specifically, the rate of acyclovir permeation is characterized by the flux (J) and the extent of acyclovir permeation is

characterized by the total cumulative amount of acyclovir permeated into the receptor solution across the study duration.

14. The flux (rate of acyclovir permeation) should be plotted as J on the Y-axis in units of mass/area/time (e.g., ng/ cm²/hr) versus time on the X-axis. Flux profiles commonly resemble plasma pharmacokinetic profiles, although the flux is a rate, rather than a concentration. The extent of acyclovir permeation should also be plotted, as the cumulative amount of acyclovir permeated on the Y-axis in units of mass/area (e.g., ng/cm²) versus time on the X-axis.
15. The flux should be calculated based upon: the receptor sample concentration (e.g., 2.0 ng/mL) at each time point; the precise, empirically measured volume of that specific diffusion cell (e.g., 6.0 mL) which may vary between individual cells; the area of dose application (e.g., 1 cm²); and the duration for which the receptor volume was accepting the acyclovir. For example, if the sample exemplified here represented a two hour period following dosing, then J would be calculated based upon the values above as:
$$J = [(2.0 \text{ ng/mL}) \times (6.0 \text{ mL})] / (1 \text{ cm}^2) / (2 \text{ hrs}) = 6 \text{ ng/cm}^2/\text{hr}$$
16. This flux should be calculated and reported for each diffusion cell for each sampling interval and plotted across the entire study duration to generate the flux profile for each diffusion cell. The rate calculated above may be plotted at the 2 hr time point, or at the midpoint between 0 and 2 hrs (i.e., 1 hr). A similar approach is utilized to calculate the cumulative total amount of acyclovir that has penetrated during each sampling interval.
17. The maximum flux (J_{max}) at the peak of the acyclovir flux profile should be compared for the test and RLD products. This is analogous to the comparison of the C_{max} for test and RLD products in the case of plasma pharmacokinetics. Similarly, the cumulative total permeation of acyclovir across the study duration should be compared for the test and RLD products: this corresponds to the area under the curve (AUC) of the incremental acyclovir permeation profile.
18. A confidence interval (CI) should be calculated for each pharmacokinetic endpoint:
 - a. the log-transformed maximum flux (J_{max})
 - b. the log-transformed total (cumulative) penetration (AUC)
19. The statistical analysis should consider a sample of n donors, for which r replicate skin sections from each one of the n donors are available for each treatment group. Each replicate (i) from each donor (j) should have been randomly assigned to each product. The two treatment groups would correspond to the test acyclovir cream 5% (T) and the RLD (R).

20. The replicate skin sections from donor 1 dosed with the test product may be denoted as T11, T21, ..., Tr1, and likewise from donor 2, T12, T22, ..., Tr2, and so forth up to n donors; T1n, T2n, ..., Trn. Similarly, the replicate skin sections dosed with the RLD product may be denoted as R1n, R2n, ..., Rrn.

21. For each donor, $I_j = \frac{1}{r} \sum_{i=1}^r (T_{ij} - R_{ij})$ should be calculated, which leads to the derivation of the point estimate,

$$\bar{I} = \frac{1}{n} \sum_{j=1}^n I_j$$

the estimate of inter-donor variability,

$$S_I^2 = \frac{1}{(n-1)} \sum_{j=1}^n (I_j - \bar{I})^2$$

and the estimate of within-reference variability:

$$S_{WR}^2 = \frac{\sum_{j=1}^n \sum_{i=1}^r (R_{ij} - \bar{R}_j)^2}{(r-1)n}$$

where \bar{R}_j is the average across all r replicates for donor J of R.

22. Under normality assumptions, the following distributional results hold:

$$\bar{I} \sim N(\mu_T - \mu_R, \frac{\sigma_I^2}{n})$$

$$\frac{(r-1)n S_{WR}^2}{\sigma_{WR}^2} \sim \chi_{(r-1)n}^2$$

and the two quantities are considered statistically independent. Furthermore, one may assume a balanced design in which no donor-by-product interaction exists.

23. The recommended statistical methodology to evaluate BE includes a mixed criterion that uses the within - reference variability as a cutoff point.

24. For $S_{WR} \leq 0.294$, the test and RLD products are declared bioequivalent if the $(1-2\alpha)$ *100% confidence interval:

$$\bar{I} \pm t_{(n-1),\alpha} * \sqrt{\frac{S_I^2}{n}}$$

is contained within the limits $[\frac{1}{m}, m]$.

25. If $S_{WR} > 0.294$, the hypotheses to be tested are:

$$H_0: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} > \theta$$

$$H_a: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

where σ_{WR}^2 is the reference population within-subject variance and θ is equal to $\frac{(\ln(m))^2}{(0.25)^2}$, and where m represents the BE limit (1.25). The aim should be to construct a $(1-\alpha)$ *100% CI for the quantity $(\mu_T - \mu_R)^2 - \theta \sigma_{WR}^2$. If the upper bound of this CI is less than or equal to zero, the null hypothesis should be rejected. Rejection of the null hypothesis, H_0 , supports BE. This criterion should be accompanied by a point estimate constraint according to which the geometric mean ratio (point estimate of the log-transformed response has to fall within the pre-specified limits: $[\frac{1}{m}, m]$).

26. One possible way to perform the analysis in order to derive the upper bound of this CI is to use an approach similar to that described in the FDA Draft Guidance on Progesterone (recommended Apr 2010; revised Feb 2011), with appropriate modifications for this replicate experimental design.

27. The method of randomization should be described in the protocol and the randomization schedule provided, preferably in a SAS data set in .xpt format (created using the SAS XPORT procedure). It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the test and RLD products dosed in the study. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each skin section.

II. Additional comments relating to the in vivo option (BE study with a clinical endpoint):

1. FDA recommends conducting a BE study with a clinical endpoint in immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (RHL) comparing the test product versus the RLD and placebo (vehicle) control with treatment initiated as early as possible following the onset of signs or symptoms of herpes labialis, i.e.,

during prodrome or no later than when herpetic lesions first appear. Treatment should be applied five times per day for 4 days (20 applications).

2. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products at the lower end of the dose/response curve.
3. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Healthy, immunocompetent male or non-pregnant, non-lactating females aged at least 18 years with recurrent herpes labialis.
 - b. At least 3 recurrences of a typical herpes labialis lesion within the past year.
 - At least half of recurrences preceded by recognizable prodromal symptoms, e.g., itching, redness, burning, tingling or a sense of irritation.
 - At least half of prodromes followed by classical lesions, e.g., ulcer, vesicle, and/or hard crust.
4. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
 - c. Subject who is unable or is not expected to reliably comprehend or satisfactorily assess a herpetic lesion.
 - d. Subject with any abnormal skin condition, e.g., acne, eczema, rosacea, psoriasis, albinism, or chronic vesiculo-bullous disorders, known to occur or currently present in the area ordinarily affected by RHL.
 - e. Current active immunodeficiency syndrome or disease.
 - f. Current active malignancy.
 - g. Current episode of herpes labialis that is not completely healed.
 - h. Recent organ transplant.
 - i. Chronic use of immunosuppressive drugs (e.g., systemic steroid) or topical steroids.
 - j. Chronic use of antiviral medication with activity against herpes simplex virus (HSV).
 - k. History of vaccination for HSV type 1 (typically oral herpes) or HSV type 2 (typically genital herpes).
 - l. History of herpes keratitis.
 - m. Candidate for parenteral antiviral treatment or for prophylactic antiviral therapy of their RHL.

- n. Contraindication to antiviral therapy or known hypersensitivity to acyclovir, valacyclovir or any component of acyclovir therapy.
 - o. Use within four weeks prior to baseline of any over-the-counter or prescription antiviral treatment.
5. A positive viral culture is not required for enrollment.
6. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
- a. Antiviral therapies, other than study product.
 - b. Corticosteroids.
 - c. Treatments for cold sores, other than study product.
 - d. Topical lip balms.
 - e. Cosmetics or other skin products applied to the treatment area.
 - f. Prolonged sun exposure (i.e., sunbathing or sunburn).
 - g. Mechanical disruption (i.e., scrubbing, lancing, shaving) of the prodromal area or lesion.
 - h. Subjects should be instructed to wash their hands with soap and water before and after applying treatment, to avoid rubbing the cold sore and to avoid contact of the study product with the eye or the inside of mouth or nose.
7. The recommended primary endpoint is the duration of episode (DOE) assessed by the investigator, based on both clinical observation and review of the subject diary, and defined as:
- a. For subjects who experience a vesicular lesion, DOE is the time from the treatment initiation to the healing of primary lesions (loss of crust; residual erythema may be present after loss of hard crust).
 - b. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last.

The primary endpoint is calculated by subtracting the recorded time of the first application of study medication in the case report from the recorded time of the investigator-assessed healing.

8. Within 24 hours (study Day 1) of initiating treatment with study drug, recommend that subjects return to study site for investigator assessments and return to study site for investigator assessments daily thereafter (or as often as possible) until:

- a. healing of the primary vesicular lesion, for those subjects who experience a vesicular lesion, OR
 - b. return to normal skin or the cessation of symptoms, whichever occurs last, for those subjects whose primary lesions are not vesicular in nature.
9. Provide subjects with a diary and instruct them to record their symptoms, such as pain, tenderness, tingling, itching, discomfort and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, ulcer, crust), at a minimum of twice daily.
10. A rescue clause is recommended to allow subjects who significantly worsen (e.g., significant increase in size or number of lesions beyond the patient's usual pattern, progression of lesions after the first few days of therapy, development of severe pain, or evidence of tissue necrosis) during therapy to be discontinued from the study and provided with standard therapy.
11. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
- a. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 1 consecutive day, and complete the evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
 - b. The mITT population includes all randomized subjects who meet all inclusion/exclusion criteria, apply at least one dose of assigned product and return for at least one post-baseline evaluation visit.
 - c. The safety population includes all randomized subjects who receive study product.
12. Subjects who are discontinued early from the study due to insufficient or lack of treatment effect after completing 3 days of treatment should be included in the PP population as treatment failures and assigned the longest time to healing observed in the study. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF) if complete healing was noted at their last visit and assigning the longest time to healing if healing was not complete at their last visit.
13. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

14. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
15. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then the sponsor must clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
16. The method of randomization should be described in the protocol and the randomization schedule provided in a SAS data set in .xpt format (created using the SAS XPORT procedure). It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
17. A detailed description of the blinding procedure is to be provided in the study protocol and final report. The packaging of the test, RLD and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
18. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
19. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

20. To establish BE, the 90% confidence interval of the test/reference ratio of the means for the primary endpoint must be contained within [0.80, 1.25] for a continuous variable, using the PP population.
21. It is recommended that an analysis of covariance (ANCOVA) with two covariates be used for the estimation of the ratio of the means. The two covariates are the type of primary lesion (vesicular or not vesicular in nature) and the baseline absolute lesion count.
22. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$) with regard to the primary endpoint, using the mITT study population.
23. To establish BE, it is recommended the following compound hypotheses be tested using the PP population:

$$H_0 : \mu_T / \mu_R < \theta_1 \text{ or } \mu_T / \mu_R > \theta_2 \text{ versus } H_A : \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$

where μ_T = mean of the primary endpoint for the test group, and
 μ_R = mean of the primary endpoint for the reference group.

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the 90% confidence interval for the ratio of the means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

24. In addition to the test described above, a supportive time-to-event (survival) statistical analysis using the Kaplan/Meier methodology and the Cox proportional hazards model can be performed for the DOE primary endpoint.
25. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - b. Provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. All SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF- modified data set).

- e. Provide a separate dataset for variables such as demographics, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

26. Provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:

- a. Study identifier
- b. Subject identifier
- c. Site identifier: study center
- d. Age
- e. Age units (years)
- f. Sex
- g. Race
- h. Name of Actual Treatment (exposure): test product, RLD, vehicle control
- i. Completed the study (yes/no)
- j. Reason for premature discontinuation of subject
- k. Subject required additional treatment for herpes labialis due to unsatisfactory treatment response (yes/no)
- l. Per Protocol (PP) population inclusion (yes/no)
- m. Reason for exclusion from PP population
- n. Modified Intent to Treat (mITT) population inclusion (yes/no)
- o. Reason for exclusion from mITT population
- p. Safety population inclusion (yes/no)
- q. Reason for exclusion from Safety population
- r. Time to complete healing of lesions (days)
- s. Treatment compliance: number of missed doses per subject
- t. Concomitant medication (yes/no)
- u. Adverse event(s) reported (yes/no)

Refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safety_rs
101	1	01	54	YEARS	F	1	A	Y		N	Y		Y		Y	
101	2	01	58	YEARS	F	1	B	Y		N	Y		Y		Y	
							tim_heal	complan	CM	AE						
							6	0	Y	Y						
							4	0	N	N						

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M=Male, F=Female, U=Unknown
RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=vehicle control
completd: Subject completed the study, e.g., Y=Yes, N=No
disc_rs: Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt: Subject required additional treatment for herpes labialis due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp: Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs: Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt: Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety: Safety population inclusion, e.g., Y=Yes, N=No

safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
tim_heal: Time to complete healing of lesions (days)
complian: Treatment compliance, e.g., number of missed doses per subject
CM: Concomitant medication, e.g., Y=Yes, N=No
AE: Adverse event(s) reported, e.g., Y=Yes, N=No

27. These in vivo BE study recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of acyclovir.