Guidance for Industry

Nonsterile Semisolid Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 1997

SUPAC-SS
CMC 7

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Table of Contents

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I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to change (1) the components or composition, (2) the manufacturing (process and equipment), (3) the scale-up/scale-down of manufacture, and/or (4) the site of manufacture of a semisolid formulation during the postapproval period. This guidance addresses nonsterile semisolid preparations (e.g., creams, gels, lotions, and ointments) intended for topical routes of administration. The guidance defines (1) the levels of change; (2) recommended chemistry, manufacturing, and controls (CMC) tests to support each level of change; (3) recommended in vitro release tests and/or in vivo bioequivalence tests to support each level of change; and (4) documentation to support the change.

The guidance specifies the application information that should be provided to the Center for Drug Evaluation and Research (CDER) to ensure continuing product quality and performance chacteristics of the semisolid topical formulation for specified changes. The guidance does not comment on or otherwise affect compliance/inspection documentation defined by the Office of Compliance in CDER or the Office of Regulatory Affairs at FDA.

The guidance provides recommendations on application documentation for the following multiple

[1] This guidance has been prepared by the Scale-Up and Post Approval Change Semisolids (SUPAC-SS) Working Group operating under the direction of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) and the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on semisolid dosage forms scale-up and postapproval changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

changes, provided appropriate test and filing documents are submitted (1) multiple level 1 changes with level 1 test and filing documentation; (2) multiple level 1 changes; one level 2 change with level 2 test and filing documentation; (3) multiple level 2 changes with level 2 test documentation and a prior approval supplement (PAS) and (4) level 3 manufacturing site change and any other level 1 change with level 3 manufacturing site change test and filing documentation. The documentation to support the changes varies depending on the type and the complexity of the semisolid dosage form. For those changes filed in a Changes Being Effected (CBE) Supplement (21 CFR 314.70(c)), the FDA may review the supplemental information and decide that the changes are not approvable. Sponsors should contact the appropriate CDER review division and staff for information about tests and application documentation for changes not addressed in this guidance, or for successive level 2 or 3 changes submitted over a short period.

The regulations provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the *Federal Register* that provides for a less burdensome notification of the change (e.g., by notification at the time a supplement is submitted or in the next annual report) (21 CFR 314.70(a)). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

II. GENERAL BACKGROUND

In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug, as well as other characteristics, such as viscosity.

A. Critical Manufacturing Parameters

For a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because dispersed matter can distribute differently depending on to which phase a particulate substance is added. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This

is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed.

Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation prior to packaging is critical and should be specifically addressed in process validation studies.

B. General Stability Considerations

The effect that SUPAC changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. For SUPAC submissions, the following points should also be considered:

1. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.

2. Where stability data show a trend towards potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

3. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see section III-VI for details) production batches, and to report the results in subsequent annual reports.

C. The Role of In Vitro Release Testing

The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, in vitro surrogate tests are often used to assure that product quality and performance are maintained over time and in the presence of change. A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, in vitro release testing has shown promise as a means to comprehensively assure consistent delivery of the active

component(s) from semisolid products.

An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products. However, there may be instances where it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the Agency. With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered.

The evidence available at this time for the in vitro-in vivo correlation of release tests for semisolid dosage forms is not as convincing as that for in vitro dissolution as a surrogate for in vivo bioavailability of solid oral dosage forms. Therefore, the Center's current position concerning in vitro release testing is as follows:

1. In vitro release testing is a useful test to assess product "sameness" under certain scale-up and postapproval changes for semisolid products.

2. The development and validation of an in vitro release test are not required for approval of an NDA, ANDA or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test.

3. In vitro release testing, alone, is not a surrogate test for in vivo bioavailability or bioequivalence.

4. The in vitro release rate should not be used for comparing different formulations across manufacturers**.**

III. COMPONENTS AND COMPOSITION

This section of the guidance focuses on changes in excipients in the drug product. Qualitative changes in excipients should include only those excipients which are present in approved drug products for the specific route of administration. Quantitative changes in excipients should not exceed the amount previously approved in products with the same specific route of administration.[2] The chronology of changes in components and composition should be provided. Changes in components or composition that have the effect of adding a new excipient or deleting an existing excipient are defined as level 3 changes (see section III.C below), except as described below. These changes generally result in the need to change the labeling.

[2] FDA, CDER, *Inactive Ingredient Guide*, 1996, Division of Drug Information Resources.

Compositional changes in preservatives are considered separately and are not included as part of the total additive effect under sections III.A, B and C.

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

- Deletion or partial deletion of an ingredient intended to affect the color, fragrance, or flavor of the drug product.

- Any change in an excipient up to 5% of approved amount of that excipient. The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1 changes in the composition. A change in diluent (q.s. excipient) due to component and composition changes in excipient may be made and is excluded from the 5% change limit.

- Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity≥95%) or change in a supplier or technical grade of any other excipient.

2. Test Documentation

a. Chemistry Documentation

Application/compendial product release requirements and stability testing.

Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation

None.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance.

Examples:

- Changes of >5% and ≤10% of approved amount of an individual excipient. The total additive effect of all excipient changes should not be more than 10%. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are acceptable and are excluded from the 10% change limit.

- Change in supplier of a structure forming excipient not covered under level 1.

- Change in the technical grade of structure forming excipient.

- Change in particle size distribution of the drug substance, if the drug is in suspension.

2. Test Documentation

a. Chemistry Documentation

Application/compendial product release requirements and executed batch records.

Stability testing: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

b. In Vitro Release Documentation

The in vitro release rate of a lot of the new/modified formulation should be

compared with that of a recent lot of comparable age of the pre-change formulation of the product. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance.

Examples:

- Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change.
- Change in crystalline form of the drug substance, if the drug is in suspension.

2. Test Documentation

a. Chemistry Documentation

Application/compendial product release requirements and executed batch records.Significant body of information available: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. In Vitro Release Documentation

The in vitro release rate of the new/modified formulation should be established as a point of reference. Under this level 3 change, in vitro release documentation is not required, but sponsors are encouraged to develop this information for use in subsequent changes under this guidance.

c. In Vivo Bioequivalence Documentation

Full bioequivalence study on the highest strength, with in vitro release/other approach on the lower strength(s).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

D. Preservative

For semisolid products, any change in the preservative may affect the quality of the product. If any quantitative or qualitative changes are made in the formulation, additional testing should be performed. No in vitro release documentation or in vivo bioequivalence documentation is needed for preservative changes.

1. Level 1 Change

a. Definition of Level

Quantitatively 10% or less change in the approved amount of preservative.

b. Test Documentation

- Application/compendial product release requirements.
- Preservative Effectiveness Test carried out at lowest specified preservative level.

c. Filing Documentation

Annual report

2. Level 2 Change

a. Definition of Level

Quantitatively greater than 10% and up to 20% change in the approved amount of preservative.

b. Test Documentation

- Application/compendial product release requirements.
- Preservative Effectiveness Test at lowest specified preservative level.

c. Filing Documentation

Changes being effected supplement.

3. Level 3 change

a. Definition of Level

Quantitatively greater than 20% change in the approved amount of preservative (including deletion) or use of a different preservative.

b. Test Documentation

- Application/compendial product release requirements.
- Preservative Effectiveness Test at lowest specified preservative level.
- Analytical method for identification and assay for new preservative.
- Validation studies to show that the new preservative does not interfere with application/compendial test.
- Executed batch records.
- Stability testing: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability

data of first production batch reported in annual report.

c. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

IV. MANUFACTURING

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment

1. Level 1 Change

a. Definition of Level

Change from nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients. Change to alternative equipment of the same design and operating principles.

b. Test Documentation

i. Chemistry Documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability testing: First production batch on long-term stability reported in annual report.

ii. In Vitro Release Documentation

None.

iii. In Vivo Bioequivalence Documentation

None.

c. Filing Documentation

Annual report (all information including long-term stability data).

2. Level 2 Change

a. Definition of Level

Change in equipment to a different design or different operating principles. Change in type of mixing equipment, such as high shear to low shear and vice versa.

b. Test Documentation

i. Chemistry Documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Significant body of information available: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

ii. In Vitro Release Documentation

The in vitro release rate of a lot of the dosage form prepared in new equipment should be compared with the release rate of a recent lot of comparable age of the product prepared using original equipment. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

iii. In Vivo Bioequivalence Documentation

None.

c. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

3. Level 3 Change

No level 3 changes are anticipated in this category.

B. Process

1. Level 1 Change

a. Definition of Level

Process changes, including changes such as rate of mixing, mixing times, operating speeds, and holding times within approved application ranges. Also, order of addition of components (excluding actives) to either oil or water phase.

b. Test Documentation

i. Chemistry Documentation

None beyond application/compendial product release requirements.

ii. In Vitro Release Documentation

None.

iii. In Vivo Bioequivalence Documentation

None.

c. Filing Documentation

Annual report.

2. Level 2 Change

a. Definition of Level

Process changes, including changes such as rate of mixing, mixing times, rate of cooling, operating speeds, and holding times outside approved application ranges for all dosage forms. Also, any changes in the process

of combining the phases.

b. Test Documentation

i. Chemistry Documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Significant body of information available: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

ii. In Vitro Release Documentation

The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the prechange process. The median in vitro release rates (as estimated by the estimated slope from each cell, see VII) of the lots prepared by the two processes should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

iii. In Vivo Bioequivalence Documentation

None.

c. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

3. Level 3 Change

No level 3 changes are anticipated in this category.

V. BATCH SIZE (SCALE-UP/SCALE-DOWN)

This guidance recommends that the minimum batch size for the NDA pivotal clinical trial batch or the ANDA/AADA biobatch be at least 100 kg or 10% of a production batch, whichever is larger. Deviations from this recommendation should be discussed with the appropriate agency review division. All scale changes should be properly validated and may be inspected by appropriate agency personnel.

A. Level 1 Change

1. Definition of Level

Change in batch size, up to and including a factor of ten times the size of the pivotal clinical trial/biobatch, where: (1) the equipment used to produce the test batch(es) are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records in annual report. Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation

None.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Changes in batch size from beyond a factor of ten times the size of the pivotal clinical trial/biobatch, where: (1) the equipment used to produce the test batch(es) are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability testing: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

b. In Vitro Release Documentation

The in vitro release rate of a lot of the scaled-up batch should be compared with the in vitro release rate of a recent lot, of comparable age, of the prechange scale. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the lots of the two scales should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

No level 3 changes are anticipated in this category.

VI. MANUFACTURING SITE

Manufacturing site changes consist of changes in location in the site of manufacture, packaging/filling operations, and/or testing for both company owned and contract manufacturing facilities and do not include any other level 2 or 3 changes, e.g., changes in scale, manufacturing (including process and/or equipment), and components or composition. New manufacturing locations should have had a satisfactory cGMP inspection within the past two years.

A stand-alone analytical testing laboratory site change may be submitted as a changes being effected supplement if the new facility has a current and satisfactory cGMP compliance profile with FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing lab. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended. No stability data are needed for a change in a stand alone analytical facility.

A. Level 1 Change

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation

None beyond application/compendial product release requirements.

b. In Vitro Release Documentation

None.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Annual report.

B. Level 2 Change

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where similar equipment, standard operating procedures, (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated executed batch records. None beyond application/compendial product release requirements.

Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation

None.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes consist of a site change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, similar equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. Changes should not be made to the manufacturing batch records except when consistent with other level 1 changes. Administrative information, location, and language translation may be revised as needed.

Any change to a new contract manufacturer also constitutes a level 3 change.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated executed batch records. Application/compendial product release requirements.

Significant body of information available: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

b. In Vitro Release Documentation

The in vitro release rate of a lot of the dosage form from the new manufacturing site should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form manufactured at the prior site. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the lots from the two sites should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

VII. IN VITRO RELEASE TEST

In vitro release is one of several standard methods which can be used to characterize performance characteristics of a finished topical dosage form, i.e., semisolids such as creams, gels, and

ointments. Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug(s) it contains should show up as a difference in drug release. Release is theoretically proportional to the square root of time ($\sqrt{t}$) when the formulation in question is in control of the release process because the release is from a receding boundary.

In vitro release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor fluid. The in vitro release methodology should be appropriately validated. Sample collection can be automated.

Aliquots removed from the receptor phase can be analyzed for drug content by high pressure liquid chromatography (HPLC) or other analytical methodology. A plot of the amount of drug released per unit area (mcg/cm^2) against the square root of time yields a straight line, the slope of which represents the release rate. This release rate measure is formulation-specific and can be used to monitor product quality. The release rate of the biobatch or currently manufactured batch should be compared with the release rate of the product prepared after a change as defined in this guidance.

One possible in vitro release study design is summarized below. Sponsors are encouraged to review the reference articles listed here.

Diffusion Cell System:

- A diffusion cell system with a standard open cap ground glass surface with 15 mm diameter orifice and total diameter of 25 mm.

Synthetic Membrane:

- Appropriate inert and commercially available synthetic membranes such as polysulfone, cellulose acetate/nitrate mixed ester, or Polytetrafluoroethylene 70 μm membrane of appropriate size to fit the diffusion cell diameter (e.g., 25 mm in above case).

Receptor Medium:

- Appropriate receptor medium such as aqueous buffer for water soluble drugs or a hydro-alcoholic medium for sparingly water soluble drugs or another medium with proper justification.

Number of Samples:

- Multiple replicates (six samples are recommended) to determine the release rate (profile) of the topical dermatological product.

Sample Applications:

- About 300 mg of the semisolid preparation is placed uniformly on the membrane and kept occluded to prevent solvent evaporation and compositional changes. This corresponds to an infinite dose condition.

Sampling Time:

- Multiple sampling times (at least 5 times) over an appropriate time period to generate an adequate release profile and to determine the drug release rate (a 6-hour study period with not less than five samples, i.e., at 30 minutes, 1, 2, 4 and 6 hours) are suggested. The sampling times may have to be varied depending on the formulation. An aliquot of the receptor phase is removed at each sampling interval and replaced with fresh aliquot, so that the lower surface of the membrane remains in contact with the receptor phase over the experimental time period.

Sample Analysis:

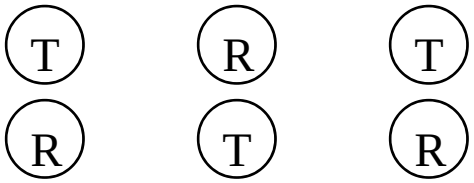
- Appropriate validated specific and sensitive analytical procedure should be used to analyze the samples and to determine the drug concentration and the amount of drug released.

In Vitro Release Rate:

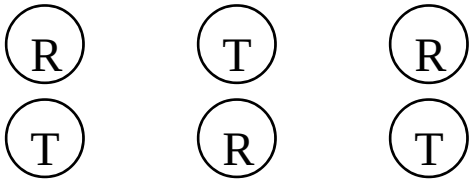
- A plot of the amount of drug released per unit membrane area (mcg/cm^2) versus square root of time should yield a straight line. The slope of the line (regression) represents the release rate of the product. An X intercept typically corresponding to a small fraction of an hour is a normal characteristic of such plots.

Design of the Rate (Profile) Comparison Study:

- The typical in vitro release testing apparatus has six cells. For each run of the apparatus, the two products being compared should be assigned to the six cells as follows:



or



where T represents the *Postchange Lot* (Test product) and R represents the *Prechange Lot* (Reference product). This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs.

- The choice of the assignment of products to cells (i.e., whether the prechange lot or the postchange lot is assigned to the "upper left corner cell" of the apparatus) may either be made systematically (i.e., alternate the pattern for each successive run) or randomly (i.e., flip a coin or use some other random mechanism).

- For the case of a nonstandard apparatus, with other than six cells, the principle of including both the prechange lot and the postchange lot in the same run should still be used. If the apparatus has only a single cell, the runs on the prechange and postchange lots should be intermixed, rather than obtaining all observations on one product followed by all observations on the other product.

Details of the In Vitro Release Comparison Test

- The in vitro release comparison should be carried out as a two-stage test.

  At the first stage, two runs of the (six cells) in vitro apparatus should be carried out, yielding six slopes (estimated in vitro release rates) for the prechange lot (R) and six slopes for the postchange lot (T). A 90% confidence interval (to be described below) for the ratio of the median in vitro release rate (in the population) for the postchange lot over the median in vitro release rate (in the population) for the prechange lot should be computed, expressed in percentage terms. If, at the first stage, this 90% confidence interval falls within the limits of 75% to 133.33%, no further in vitro testing is necessary.

  If the test is not passed at the first stage, 4 additional runs of the (six cells) in vitro apparatus should be carried out, yielding 12 additional slopes for each product, or 18 in all (including the first-stage results). The 90% confidence interval (to be described below) should be computed using all 18 slopes for each product, including the first-stage results. At the second stage, this 90% confidence interval should fall within the limits of 75% to 133.33%.

Computation of Confidence Interval - an Example:

- Because outliers are expected to occur on occasion with this testing (for example, due to an air bubble between the product sample and the membrane), a nonparametric

method is proposed, whose performance tends to be resistant to the presence of outliers. The computations are illustrated in the following example:

Suppose that the slope data obtained at the first stage are as follows:

Postchange Lot (T)	Prechange Lot (R)
1.3390	1.1331
1.3496	1.1842
1.4946	1.0824
1.4668	1.3049
1.1911	1.0410
1.2210	1.2419

The first step in the computation of the confidence interval is to form the 36 (= 6 x 6) individual T/R ratios. This is illustrated in the following table, where the prechange lot slopes (R) are listed across the top of the table, the postchange lot slopes (T) are listed down the left margin of the table, and the individual T/R ratios are the entries in the body of the table:

	1.1331	1.1842	1.0824	1.3049	1.0410	1.2419
1.3390	1.1817	1.1307	1.2371	1.0261	1.2863	1.0782
1.3496	1.1911	1.1397	1.2469	1.0343	1.2964	1.0867
1.4946	1.3190	1.2621	1.3808	1.1454	1.4357	1.2035
1.4668	1.2945	1.2386	1.3551	1.1241	1.4090	1.1811
1.1911	1.0512	1.0058	1.1004	0.9128	1.1442	0.9591
1.2210	1.0776	1.0311	1.1280	0.9357	1.1729	0.9832

The second step in the computation of the confidence interval is to order these 36 individual T/R ratios from lowest to highest:

0.9128 0.9357 0.9591 0.9832 1.0058 1.0261 1.0311 1.0343 **...** 1.2863 1.2945

1.2964 1.3190 1.3551 1.3808 1.4090 1.4357.

In the third step, the ***eighth*** and ***twenty-ninth*** ordered individual ratios are the lower and upper limits, respectively, of the 90% confidence interval for the ratio of the median in vitro release rate (slope) for T over the median in vitro release rate for R. In the example, this confidence interval is 1.0343 to 1.2863, or in percentage terms,

103.43% to 128.63%.

Because this confidence interval falls within the limits of 75% to 133.33%, the product passes at the first stage.

If the product had not passed at the first stage, an additional 4 runs would have been carried out, yielding 12 additional slopes per lot, for a total of 18 slopes per lot altogether (including the first-stage slopes).

All 324 (= 18 x 18) individual T/R ratios would be obtained, and these would be ranked from lowest to highest. It should be evident that even the computations at the first stage would be tedious to do by hand, and doing the computations at the second stage by hand is infeasible. A computer should be used.

At the second stage, the ***110th*** and the ***215th*** ordered individual ratios are the lower and upper limits, respectively, of the 90% confidence interval for the ratio of the median in vitro release rate (slope) for T over the median in vitro release rate for R. If this confidence interval falls within the limits of 75% to 133.33%, the product passes the test at the second stage.

Further Remarks on the In Vitro Release Comparison Test

- The statistical test described above is based on a standard confidence interval procedure related to the Wilcoxon Rank Sum/Mann-Whitney rank test, applied to the log slopes. References to this confidence interval procedure include:

  Conover, W.J., *Practical Nonparametric Statistics* (Second Edition), John Wiley & Sons, page 223ff, 1980.

  Hollander, M. and D.A.Wolfe, *Nonparametric Statistical Methods*, John Wiley & Sons, page 78ff, 1973.

  However, as was seen in the example, it is not necessary to actually compute logs in order to carry out the test.

- The example illustrates the case of full data, i.e., where there are 6 slopes per lot at the

first stage and, if the second stage is necessary, 18 slopes per lot at the second stage. If slopes are missing, the computations will need to be modified. For example, if a single slope were missing from one of the lots (it does not matter if it is the prechange lot or the postchange lot) at the first stage, there would only be 30 (= 5 x 6) individual T/R ratios, and the limits of the 90% confidence interval would no longer be the eighth and twenty-ninth ordered individual T/R ratio, but rather would be the sixth and twenty-fifth ordered individual T/R ratio. If data are missing at either stage of the test, the correct computation should be determined either by reference to a statistical text or consultant, or by consultation with CDER staff.

- The statistical procedure as described above does not take the block structure of the test (i.e., the fact that data are obtained in runs of six slopes at a time, rather than all at once) into account. This is justified by the following:

    1. In vitro release data available to the Center at this time show no evidence of an important run-to-run effect.

    2. The proposed experimental design, in which both products are included in each run, will help to ensure unbiasedness if a run-to-run effect should occur.

VIII. IN VIVO BIOEQUIVALENCE STUDIES

The design of in vivo bioequivalence studies for semisolid dosage forms varies depending on the pharmacological activity of the drug and dosage form. A brief general discussion of such tests follows.

Objective:

To document the bioequivalence of the drug product for which the manufacture has been changed, as defined in this guidance, compared to the drug product manufactured prior to the change or compared to the reference listed drug (RLD).

Design:

The study design is dependent on the nature of the active drug. The bioequivalence study can be a comparative skin blanching study as in glucocorticoids (FDA, *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*, June 2, 1995.) or a comparative clinical trial or any other appropriate validated bioequivalence study (e.g., dermatopharmacokinetic study) for the topical dermatological drug product.

Analytical Method:

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

GLOSSARY OF TERMS[3]

Approved Target Composition: The components and amount of each ingredient for a drug product used in an approved pivotal clinical study or bioequivalence study.

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits. (21 CFR 210.3(b)(2)).

Contiguous Campus: Contiguous or unbroken site or a set of buildings in adjacent city blocks.

Creams/Lotions: Semisolid emulsions that contain fully dissolved or suspended drug substances for external application. Lotions are generally of lower viscosity.

Diluent: A vehicle in a pharmaceutical formulation commonly used for making up volume and/or weight (e.g., water, paraffin base).

Drug Product: A drug product is a finished dosage form (e.g., cream, gel, or ointment) in its marketed package. It also can be a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug Release: The disassociation of a drug from its formulation thereby allowing the drug to be distributed into the skin or be absorbed into the body where it may exert its pharmacological effect.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Emulsion: Emulsions are two phase systems in which an immiscible liquid (dispersed phase) is dispersed throughout another liquid (continuous phase or external phase) as small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentration in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalesce. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification upon mixing. Emulsifying agents substantially prevent or delay the time needed for emulsion

[3] See Workshop Report: Scale-up of liquid and semi-solids disperse systems. G. A. Van Buskirk, V. P. Shah, D. Adair, et al. *Pharmaceutical Research*, 11, 1216-1220, 1994,

droplets to coalesce. Emulsification is the act of forming an emulsion. Emulsification can involve the incorporation of a liquid within another liquid to form an emulsion or a gas in a liquid to form a foam.

Formulation: A listing of the ingredients and quantitative composition of the dosage form.

Gel: A semisolid system in which a liquid phase is constrained within a three dimensional, cross-linked matrix. The drug substance may be either dissolved or suspended within the liquid phase.

Homogenization: A method of atomization and thereby emulsification of one liquid in another in which the liquids are pressed between a finely ground valve and seat under high pressure (e.g., up to 5,000 psi).

Internal phase: The internal phase or the dispersed phase of an emulsion comprises the droplets that are found in the emulsion.

In Vitro Release Rate: Rate of release of the active drug from its formulation, generally expressed as amount/unit area/time$^{0.5}$.

Ointment: An unctuous semisolid for topical application. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water soluble ointments may be formulated with polyethylene glycol.

Pilot Scale Batch: The manufacture of drug product by a procedure fully representative of and simulating that intended to be used for full manufacturing scale.

Preservative: An agent that prevents or inhibits microbial growth in a formulation to which it has been added.

Process: A series of operations, actions and controls used to manufacture a drug product.

Scale-up: The process of increasing the batch size.

Scale-down: The process of decreasing the batch size.

Shear: A strain resulting from applied forces that cause or tend to cause contiguous parts of a body to slide relative to one another in direction parallel to their plane of contact. In emulsification and suspensions, the strain produced upon passing a system through a homogenizer or other milling device.

- Low shear: Processing in which the strain produced through mixing and/or emulsifying shear is modest.

- High shear: Forceful processes which, at point of mixing or emulsification place a great strain on the product. Homogenization, by its very nature, is a high shear process which leads to a small and relatively uniform emulsion droplet size. Depending on their operation, mills and mixers are categorized as either high shear or low shear devices.

Significant Body of Information: A significant body of information on the stability of the product is likely to exist after five years of commercial experience for new molecular entities , or three years of commercial experience for new dosage forms.

Structure Forming Excipient: An excipient which participates in the formation of the structural matrix which gives an ointment, cream or gel etc., its semisolid character. Examples are gel forming polymers, petrolatum, certain colloidal inorganic solids (e.g., bentonite), waxy solids (e.g., cetyl alcohol, stearic acid), and emulsifiers used in creams.

Strength: Strength is the concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard) (21 CFR 210.3(b)(16)). For semisolid dosage forms the strength is usually stated as a weight/weight (w/w) or weight/volume (w/v) percentage.

Suspending agent: An excipient added to a suspension to control the rate of sedimentation of the active ingredients.

Technical grade: Technical grades of excipients differ in their specifications and intended use. Technical grades may differ in: (1) specifications and/or functionality, (2) impurities, and (3) impurity profiles.

Validation: A procedure to establish documented evidence that provides a high degree of assurance that a specific process or test will consistently produce a product or test outcome meeting its predetermined specifications and quality attributes. A validated manufacturing process or test is one that has been proven to do what it purports or is represented to do. The proof of process validation is obtained through collection and evaluation of data, preferably beginning with the process development phase and continuing through the production phase. Process validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, personnel), but it also includes the control of the entire processes for repeated batches or runs.

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Table 1 - Components and Composition

Level	Change	Test Documentation	Filing Documentation
1	• Deletion or partial deletion of color, fragrance, or flavor • Up to 5% change in approved amount of an excipient with the total additive effect of all excipient changes ≤5% • Supplier of structure forming excipient that is primarily a single chemical entity (purity ≥ 95%) or change in supplier or technical grade of any other excipient	• Application/compendial product release requirements • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability data)
2	• Change of >5% and ≤10% of approved amount of an excipient with the total additive effect of all excipient changes ≤10% • Change in supplier of a structure forming excipient (not covered under level 1) • Change in technical grade of a structure forming excipient • Change in particle size distribution of the drug substance, if the drug is in suspension	• Application/compendial product release requirements • Executed batch records • Stability: One batch with three months accelerated stability data and first production batch on long-term stability • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Table 1 - Components and Composition (cont.)

Level	Change	Test Documentation	Filing Documentation
3	• Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change • Change in crystalline form of the drug substance, if the drug is in suspension	• Application/compendial product release requirements • Executed batch records • Stability: Significant body of information available: One batch with three months accelerated stability data and first three production batches on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability • In vitro release test (encouraged only) • In vivo bioequivalence test	• Prior approval supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 2 - Components and Composition - Preservative

Level	Change	Test Documentation	Filing Documentation
1	• Quantitatively 10% or less change in the approved amount of preservative	• Application/compendial product release requirements • Preservative effectiveness test at lowest specified preservative level	• Annual report
2	• Quantitatively greater than 10% and up to 20% change in the approved amount of preservative	• Application/compendial product release requirements • Preservative effectiveness test at lowest specified preservative level	• Changes being effected supplement
3	• Quantitatively greater than 20% change in the approved amount of preservative (including deletion) or use of a different preservative	• Application/compendial product release requirements • Executed batch records • Preservative effectiveness test at lowest specified preservative level • For new preservative: analytical method for identification and assay; validation studies showing new preservative does not interfere with application/compendial tests • Stability: One batch with three months accelerated stability data and first production batch on long-term stability	• Prior approval supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 3 - Manufacturing Equipment

Level	Change	Test Documentation	Filing Documentation
1	• Nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients • Alternative equipment of same design and operating principles	• Application/compendial product release requirements • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability)
2	• Equipment of a different design or different operating principles • Type of mixing equipment: e.g., high shear to low shear or vice versa.	• Application/compendial product release requirements • Executed batch record • Stability: Significant body of information available: One batch with three months accelerated stability data and first production batch on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 4 - Manufacturing Process

Level	Change	Test Documentation	Filing Documentation
1	• Process changes within approved applications ranges • Order of addition of components (excluding actives)	• Application/compendial product release requirements	• Annual report
2	• Process changes outside approved application ranges • Process of combining phases	• Application/compendial product release requirements • Executed batch record • Stability: Significant body of information available: One batch with three months accelerated stability data and first production batch on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 5 - Batch Size

Level	Change	Test Documentation	Filing Documentation
1	• Change in batch size up to and including ten times the size of the pivotal clinical trial/biobatch	• Application/compendial product release requirements • Executed batch records • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability data)
2	• Change in batch size beyond a factor of ten times the size of the pivotal clinical trial/biobatch	• Application/compendial product release requirements • Executed batch records • Stability: One batch with three months accelerated stability data and first production batch on long-term stability • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 6 - Manufacturing Site Change

Level	Change	Test Documentation	Filing Documentation
1	• Within a single facility	• Application/compendial product release requirements	• Annual report
2	• Within the same contiguous campus or between facilities in adjacent city blocks	• Application/compendial product release requirements • Executed batch records • Location of new site • Stability: First production batch on long-term stability	• Changes being effected supplement • Annual report (long-term stability data)
3	• Different campus • Contract manufacturer	• Application/compendial product release requirements • Executed batch record • Location of new site • Stability Significant body of information available: One batch with three months accelerated stability data and first three production batches on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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