الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

SFDA's guidance on the Equivalence of Topical Products

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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***Disclaimer**: This guidance helps applicants meet the expectations of regulators. This guidance should not be understood as being legally enforceable. The applicant can use another approach if the approach satisfies the requirements of the SFDA guidelines for bioequivalence.*

OBJECTIVE

To further facilitate generic pharmaceutical topical product availability and to support the generic pharmaceutical industry with identifying the most appropriate requirements and methodologies for in-vitro studies of topical products which in turn aids in meeting SFDA expectations.

DEFINITIONS AND TERMS

Generic pharmaceutical product:
It is a medication developed to be the same as reference product in dosage form, safety, efficacy strength, route of administration, quality, performance characteristics, and intended use.

Reference product:
Pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product would normally be the innovator product for which efficacy, safety and quality have been established.

Selection of reference product:
Reference Product must be the original brand-name (i.e. manufactured in the country of origin of the original brand name); if this is not available in the local market then the brand-name regarding the same company but different country of origin is used, marketed in GCC region, ICH region, or in any stringent regulatory. If the original brand-name is not available in the market or no longer produced, then the product which is the local market leader may be used as a reference product.

Q1:
The excipient composition of the test product is qualitatively the same as the reference product.

Q2:
The excipient composition of the test product is quantitatively the same as the reference product.

Q3:
The test products having a similar microstructure based on the similarity of physicochemical properties. Such properties may include molecular weight, partition coefficient, melting point (boiling point if applicable), pKa, sensitivity to light, air, or moisture, degradation pathway, solubility, and pH effects, as well as particle size and polymorphism if the active substance is present in the solid state in the drug product.

IVRT:
In Vitro Release Test study which is a sensitive, discriminating compendial method with

established statistical analyses that are used to evaluate the rate and extent of release of an active substance in the proposed formulation.

IVPT:
In Vitro Permeation Test is a study that assesses the rate and extent to which an active ingredient from a topical product becomes available at or near a site of action (i.e. the skin), and may be used to characterize and compare the rate and extent of bioavailability for an active ingredient from a test topical product and its reference product.

SCOPE

The guidance relates to locally applied acting medicinal products. The equivalence guidance is applicable to certain cases of demonstration of equivalence of a generic locally applied acting medicinal product with an existing medicinal product.

This addresses equivalence testing of specific topical products to support a claim of therapeutic equivalence with comparator medicinal products, in lieu of therapeutic equivalence clinical trials. Aspects relating to quality, efficacy, and safety are discussed.

This approach is not applicable and clinical therapeutic equivalence studies are in principle required for the following drug products:

- With a narrow therapeutic index.
- With dose related, systemic toxicity, except in those cases where equivalent systemic exposure is shown by conventional pharmacokinetic bioequivalence studies.
- Where the means e.g. dissolution, release, diffusion, and permeation kinetics by which the active substance reaches the local site of action is not established or understood.
- Where the method of administration is not the same.
- That cannot be fully characterized with respect to quality attributes e.g. due to complex formulation, methodological limitations.
- Where it is not possible to measure a quantifiable permeation kinetic or pharmacodynamic event e.g. due to limited diffusion or insensitive tests.
- Where *in vitro* and *in vivo* permeation kinetic and pharmacodynamic studies are not applicable or considered insufficiently predictive of clinical response e.g. products indicated for the treatment of open wounds and ulcers.
- Vasoconstrictor topical products where vasoconstrictions studies could be done to support the equivalence between test and reference topical formulation.

GENERAL REQUIREMENTS

These requirements applied for topical products listed in Table 1.

Equivalence with respect to quality (extended pharmaceutical equivalence)

Pharmaceutical form, qualitative and quantitative composition, microstructure/physical properties, product performance e.g. dissolution, in vitro release test, and method of administration should be compared.

Product quality equivalence should be undertaken on batches representative of the product to be marketed and the manufacturing process – i.e. batches at production scale. Alternatively, pilot scale batches, at least 1/10 production scale may be used for characterization and comparative purposes, if there are no changes in the manufacturing process and equipment, and evidence provided that scale-up does not affect product quality.

It is acknowledged that there may be only a limited number of representative batches available at the time of submission, and at least three different batches of both the test and comparator products should be compared.

To enable statistical evaluation, the number of samples should be at least 12 units per batch for each experiment.

Extended pharmaceutical equivalence acceptance criteria

The extended pharmaceutical equivalence acceptance criteria between the test and comparator medicinal product are:

A. Pharmaceutical form

The drug product should be the same pharmaceutical form, with the same solution state of the active substance in the same immiscible phases.

B. Qualitative and Quantitative Composition

- The active substance content and its salt form should be the same.
- In general, the excipients qualitative composition, including grade, if necessary, and quantitative composition of excipients should be the same, although some exceptions are permitted.

  In particular, excipients whose function is to influence the active substance solubility, thermodynamic activity or bioavailability and product performance should be qualitatively the same.

  The nominal quantitative composition of the excipients should be the same or differences not greater than ±5%. For example, for an excipient present in the comparator medicinal product at 2%w/w, the permitted range in the test product is 1.9 – 2.1%w/w.
- A permitted exception for a qualitatively different excipient may be acceptable for:
  - Excipients whose primary function is not related to product performance or administration, i.e. antioxidants, antimicrobial preservatives, colours, and do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance.

Well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed.

- Excipient paraffin homologues may be acceptable for excipients whose function relates to the vehicle or emolliency, and do not influence the active substance solubility, thermodynamic activity or bioavailability and product performance.
  The different excipient should have no effect on local tolerance or safety. It should be shown that the excipients do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance. In these cases, a biowaiver cannot be justified and is not permitted.

- A permitted exception for a quantitative difference of not greater than ±10% is acceptable:
  - For excipients whose function only relates to the vehicle properties or emolliency.
  - For excipients whose function is not related to product performance or administration, i.e. antioxidants, antimicrobial preservatives, colours.
    It should be shown that the excipients do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance.

C. Acceptance Criteria

- For quantitative quality characteristics, the 90% confidence interval for the difference of means of the test and comparator products should be contained within the acceptance criteria of +/- 10% of the comparator product mean, assuming normal distribution of data.
- Qualitative quality characteristics should be essentially the same.

D. Administration

- The method of administration and administration devices should be similar and achieve the same dose on application.
- If applicable, when product transformation occurs following administration, the test and comparator medicinal product residues are equivalent with respect to quality i.e. in terms of extended pharmaceutical equivalence.

Strength Biowaiver

If several strengths of a test product are applied for, it may be sufficient to establish equivalence at only one strength, which is most sensitive to detect potential differences between formulations.

The following requirements must all be met where a waiver for additional strength(s) is claimed:

a) The different strengths of the test products are manufactured by the same manufacturing process.
b) The different strengths of the test products have the same qualitative composition.
c) The qualitative and quantitative compositions of the different strengths of the test products are equivalent to the different strengths of the comparator medicinal products.
d) Extended pharmaceutical equivalence is demonstrated between the test and comparator medicinal product for all strengths.

Table 1: Specific In vitro requirements for each product:

Number	Active ingredient; Form/Route	The requirements between the proposed Test and the Reference products are shown by bullet point.				
		Q1	Q2	Q3*	IVRT	IVPT
1.	Acyclovir Ointment; topical	●	●	●	●	
2.	Acyclovir Cream; topical	●	●	●	●	●
3.	Bexarotene Gel; topical	●	●	●	●	
4.	Calcipotriene Solution; Topical	●	●	●		
5.	Calcipotriene Cream; topical	●	●	●	●	●
6.	Calcipotriene Ointment; topical	●	●	●	●	●
7.	Ciclopirox Solution; Topical	●	●	●		
8.	Ciclopirox Shampoo; Topical	●	●	●		
9.	Clindamycin phosphate Gel; Topical	●	●	●	●	
10.	Clindamycin phosphate solution; Topical	●	●	●		
11.	Clindamycin phosphate Swab; Topical	●	●			
12.	Clindamycin phosphate Aerosol, Foam; Topical	●	●	●		
13.	Clotrimazole Solution; Topical	●	●	●		
14.	Crotamiton Cream; Topical			●		
15.	Crotamiton Lotion; Topical			●		
16.	Docosanol Cream; topical	●	●	●	●	
17.	Efinaconazole Solution; Topical	●	●	●		
18.	Erythromycin Gel; topical			●		
19.	Erythromycin Solution; Topical	●	●			
20.	Erythromycin Swab; Topical	●	●			
21.	Fluocinolone acetonide Cream; Topical			●		
22.	Fluorouracil Solution; Topical	●	●	●		
23.	Gentamicin Sulfate Ointment; Topical			●		
24.	Gentamicin Sulfate Cream; Topical			●		
25.	Glycopyrronium tosylate Cloth; Topical	●	●			
26.	Hydrogen peroxide Solution; Topical	●	●	●		

27.	Ivermectin Lotion; Topical	●	●	●	●	
28.	Lidocaine Ointment; Topical	●	●	●	●	
29.	Luliconazole Cream; Topical	●	●	●	●	
30.	Malathion Lotion; Topical	●	●			
31.	Metronidazole Cream; Topical	●	●	●	●	●
32.	Metronidazole Gel; Topical	●	●	●	●	
33.	Metronidazole Lotion; Topical	●	●	●	●	●
34.	Minoxidil Aerosol; foam; Topical	●	●			
35.	Minoxidil Solution; Topical	●	●			
36.	Nystatin Ointment; Topical			●		
37.	Nystatin Cream; Topical			●		
38.	Nystatin Powder; Topical			●		
39.	Nystatin; Triamcinolone acetonide Cream; Topical			●		
40.	Nystatin; Triamcinolone acetonide Ointment; Topical			●		
41.	Oxymetazoline hydrochloride Cream; Topical	●	●	●	●	●
42.	Ozenoxacin Cream; Topical	●	●	●	●	●
43.	Penciclovir Cream; Topical	●	●	●	●	●
44.	Pimecrolimus Cream; Topical	●	●	●	●	●
45.	Podofilox Solution; Topical	●	●	●		
46.	Podofilox Gel; Topical	●	●	●	●	
47.	Silver sulfadiazine Cream; Topical	●	●	●	●	
48.	Spinosad Suspension; Topical	●	●	●	●	
49.	Tavaborole Solution; Topical	●	●	●		
50.	Tacrolimus Ointment; Topical	●	●	●	●	●
51.	Tretinoin Gel; Topical	●	●	●	●	
52.	Tretinoin Solution; Topical	●	●	●		
53.	Triamcinolone acetonide Lotion; Topical			●		
54.	Triamcinolone acetonide Ointment; Topical			●		
55.	Triamcinolone acetonide Cream; Topical			●		

- (*) Follow the comparative physicochemical characterizations test mentioned in the US-FDA Guidance for Physicochemical and Structural (Q3) Characterization of Topical Drug Products.
- There are some exceptions regarding the differences in the quantitative compositions and discussed generally in this guideline.
- For more information on how to perform the *in-vitro* release test (IVRT) please see Annex 1.
- The waiver of *in-vivo* requirements may not be accepted when not adhering to the above requirements for the specific product may subject the product to additional requirements.

Annex 1: In vitro release test (IVRT)

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 when a change is done.

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.

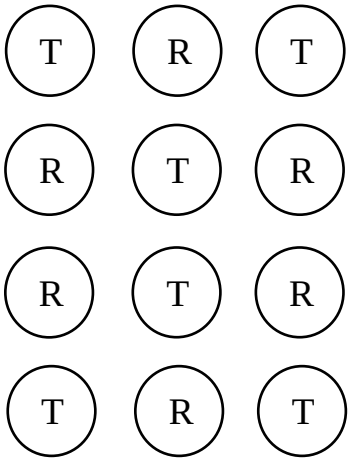
Sampling Time:
Multiple sampling times (at least 5 times) over an appropriate time period to generate an adequate release profile and to determine the drug release rate (a 6-hour study period with not less than five samples, i.e., at 30 minutes, 1, 2, 4 and 6 hours) are suggested. The sampling times 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.

Annex 2: In vitro permeation test studies (IVPT)

Refer to In Vitro Permeation Test Studies for Topical Drug Products by FDA.

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