General Considerations for the "No Significant Difference" Evaluation of a Proposed Generic Formulation

FDA-CRCG Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons

Session 2: Qualitative and Quantitative Considerations for Formulation Assessments

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Inactive Ingredients in Topical Products

- Title 21 of the CFR, Sections 314.94(a)(9)(v) and 320.22
  - An ANDA for a drug product intended for topical use may include different inactive ingredients compared to the RLD provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.
    - A topical test product is **not required by regulation to be qualitative (Q1) and quantitatively (Q2) the same** as the RLD.
  - In vivo bioequivalence may be self-evident for a topical solution or solution-based foam aerosol if, among other things:
    - The test product contains ***"no inactive ingredient or other change in formulation …that may significantly affect systemic or local availability"***
    - **Includes but does not require Q1 and Q2 sameness**

CFR: Code of Federal Regulations; ANDA: Abbreviated new drug application; RLD: Reference listed drug

Challenges with Q1/Q2 Sameness

- Implementing Q1/Q2 sameness can be challenging for generic topical products:
  - Discontinuation of the RLD product
  - Formulation of RS may be different compared to RLD
  - Changes to the RS formulation over time
  - Use of quantity sufficient (q.s.) for inactive ingredients
- A sophisticated assessment of the formulation can ensure that the test product is well-matched to the RS.

RS: Reference standard

“No Significant Difference” Standard

- A topical test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the RS that may significantly affect the local or systemic availability of the active ingredient.
  - For example, a test topical product that is Q1 and Q2 the same as the RS implicitly has **no significant difference (NSD)** compared to the RS.

RS: Reference standard

“No Significant Difference” Standard

- The intent of a NSD assessment is to determine whether the formulation of the test product is sufficiently well-matched to the RS.
- The goal is to adequately mitigate the risk associated with potential failure modes for BE associated with differences in the formulation.
  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Vehicle contribution to efficacy
  - Stability and solubility of the drug

RS: Reference standard; BE: bioequivalence

Q1/Q2 Sameness vs. NSD Standard

- NSD is based upon the principles for assessing Q1/Q2 sameness, but also considers certain differences that have previously been determined to be acceptable based on available scientific evidence
- Certain minor differences in components and composition may also be acceptable based upon:
  - Information available to the Agency
  - Evidence submitted in an ANDA (e.g., evidence to demonstrate NSD between the test and RS in the local or systemic availability of the active ingredient)
- Does not mean that any formulation would be acceptable

Recent Changes to Topical PSGs

Previous version

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]

Current version (Oct 2022)

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for acyclovir topical cream, 5% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

Assessment in Relation to the RS

- When the RLD for a topical product is discontinued, it may not be feasible to ascertain its Q1 and Q2.
- The RS product may not be Q1 or Q2 the same as the RLD product.
- A test product may be assessed with respect to the RS formulation.
  - If the RS is used, an ANDA for a drug product intended for topical use still has to meet requirements under 21 CFR 314.94(a)(9)(v)

RLD: Reference listed drug; RS: Reference standard

Assessment in Relation to RS Changes

Challenge

- The composition of the RS product may change after the original approval (i.e., in a supplement).
- Should the test formulation be assessed against the original formulation or the current formulation for the RS?
  - The original formulation of the RS contained 5% w/w of mineral oil, but the current formulation of the RS contains 6% w/w.
  - Safety and efficacy studies were not necessary to support the change in formulation.

NSD

- The acceptable range of the affected inactive ingredient should include the entire range found to be acceptable for the RS product.
  - The RS product is treated as having a range 5-6% w/w of mineral oil. A test product may be suitable if it contains 4.73-6.33% w/w of mineral oil.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Ingredient Grade

Challenge

- The RS may contain a specific grade of an inactive ingredient.
  - Is Carbomer homopolymer Type B (Carbopol 974P) the same as Carbopol 934P?
  - Is White Petrolatum, USP the same as Petrolatum, USP?

NSD

- A topical test product may be considered to have NSD if it contains minor differences in ingredient grade.

RS Formulation		Test Formulation	
Carbopol 934P	2.00%	Carbomer homopolymer type B, NF (Carbopol 974P)	2.00%
Petrolatum, USP	5.00%	White Petrolatum, USP	5.00%

- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Sub-Components

Challenge

- Some inactive ingredients are comprised of a mixture of sub-components.
- The RS may use a proprietary ingredient that is a pre-blended mixture of specific quantitative amounts of sub-components.
  - The RS contains 1% w/w of ingredient X, which is a pre-blended mixture that contains 25:75 ratio of sub-component A:B.

NSD

- A topical test product may be considered to have NSD if it contains the same quantitative amounts of each sub-component, rather than using the proprietary ingredient.

RS Formulation		Test Formulation	
Ingredient X	1.00%	Sub-component A	0.25%
		Sub-component B	0.75%

- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Sub-Components

Challenge

- Some inactive ingredients are comprised of a mixture of sub-components.
- The RS may use a proprietary ingredient that is a pre-blended mixture of variable quantitative amounts of sub-components.
  - The RS contains 1% w/w of ingredient X, which is a pre-blended mixture that contains 40-60% of sub-component A and 40-60% of sub-component B.

NSD

- A test product may be considered to have NSD if it contains quantitative amounts of each sub-component within the ranges that were found acceptable for the RS.

RS Formulation		Test Formulation #1		Test Formulation #2	
Ingredient X	1.00%	Sub-component A	0.40%	Sub-component A	0.60%
		Sub-component B	0.60%	Sub-component B	0.40%

- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Ingredient Form

Challenge

- Some inactive ingredients exists in different forms (e.g., hydration forms).
- The RS may use Edetate Disodium, USP, which may exist in a dihydrate form or an anhydrous form.

NSD

- A test product may be considered to have NSD if it contains a different form of the ingredient, with adjustments to the quantitative amount of the pure ingredient and water.

RS Formulation		Test Formulation	
Edetate disodium, USP (dihydrate)	0.05%	Edetate disodium, USP (anhydrous)	0.045%

- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Ingredient Purity

Challenge

- Some inactive ingredients exists in different purities.
- The RS may use Alcohol, USP, which is comprised of alcohol equivalent to 73.5% (w/w) alcohol as 95% alcohol (v/v).

NSD

- A test product may be considered to have a NSD if it contains a different purity of the ingredient, with adjustments to the quantitative amount of the pure ingredient and water.

RS Formulation		Test Formulation	
Alcohol USP (95% v/v)	73.5%	Dehydrated alcohol USP (99% v/v)	67.0%

- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Color or Fragrance

Challenge

- Some RS products contain an ingredient that is added for coloring or fragrance purposes, which may be challenging for a test product to match.

NSD

- A test product may be considered to have NSD if it contains a contains a different color or fragrance than the RS, if it does not affect the bioavailability of the active ingredient and/or affect the safety of the drug product.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of pH Modifier

Challenge

- The single point nominal amount of a pH modifier in the RS composition table may not reflect the quantitative range or may be specified as a quantity sufficient (q.s.) to achieve a target pH for the RS.

NSD

- A test product may be considered to have NSD if it does not contain the same nominal amount of a pH modifier, as long as the pH and other relevant characteristics of the test and RS match.

RS Formulation (pH 5.2)		Test Formulation	
Sodium hydroxide, USP	0.10%	Sodium hydroxide, USP	0.20% (adjust to pH 5.2)

- The acceptability of such difference would be determined during ANDA assessment.

Example of a NSD product

RS Formulation	
Ingredients	**% w/w**
Tanasone, USP (active ingredient)	0.25
Petrolatum, USP	15.00
Mineral Oil, USP	2.00
Cetostearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Paramix® *	0.12
Sodium Hydroxide, NF	0.03 (pH 5.5)
Benzyl Alcohol, NF	1.00
Purified Water, USP	57.00
*Mixture of methylparaben, USP and propylparaben, USP (1:1)	

Test Formulation	
Ingredients	**% w/w**
Tanasone, USP (active ingredient)	0.25
White Petrolatum, USP	15.00
Mineral Oil, USP	2.00
Cetostearyl Alcohol, NF	12.5
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Monohydrate, USP	0.265
Methylparaben, USP	0.06
Propylparaben, USP	0.06
Sodium Hydroxide, NF	q.s. to target pH 5.5
Benzyl Alcohol, NF	1.00
Purified Water, USP	q.s. to 100% (~56.525)

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious product is not representative of a complete and accurate FDA approved drug product.

Formulation assessment requests

- Consider including the following, along with your proposed formulation:
  - Proprietary names and/or certificate of analysis for inactive ingredients available in different purities/grades (e.g., alcohol, polymers, etc.)
  - Reverse engineering data to support the proposed levels of inactive ingredients in a test formulation
    - When the reverse engineering data appears to be higher compared to the nominal levels reflected in the Inactive Ingredient Database (IID)
    - Inactive ingredients with small concentrations
    - Complex inactive ingredients (e.g., mixture with subcomponents)
  - For inactive ingredients added on a q.s. basis during the manufacturing process (e.g., pH modifiers), identify as such in the formulation table and provide scientific rationale for the target values that you would utilize (e.g., target pH).

Summary

- Generic topical products are not required to be Q1/Q2 the same.
- The intent of a NSD assessment is to determine whether the formulation of the test product is sufficiently well-matched to the RS.
- A NSD standard expands the eligibility for a characterization-based BE approach for topical products, while preserving the scientific principles of Q1/Q2 sameness that are critical to mitigate the risks associated with potential failure modes for BE.

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Questions?

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