Navigating Formulation Assessment: *Considerations for Products that are Not Required to be Q1Q2*

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Navigating Controlled Correspondences to
Support Generic Drug Development

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Overview

- Identify scenarios where obtaining the Agency's feedback on formulation aspects may be beneficial during generic product development
- Describe information to include in a controlled correspondence (CC) and avoid pitfalls

Inactive Ingredients in Topical Products

- Title 21 of the CFR, Sections 314.94(a)(9)(v)
  - 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.

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

Typical BE Approaches for Topical Products

- Comparative Clinical Endpoint (CCEP) BE Study
- Vasoconstrictor (VC) BE Study
- Waiver of In Vivo BE Study
- Characterization-Based BE Approach

Feedback on Formulation: MDE Assessment

- Information available in the IID can be helpful towards formulation design

- Consider context of use when selecting concentration of inactive ingredients
  - Route of administration — Listed in the IID
  - Duration of use
  - Patient population

  } Not included in the IID

MDE: Maximum Daily Exposure; IID: Inactive Ingredient Database
FDA's Inactive Ingredient Database website

Feedback on Formulation: MDE Assessment

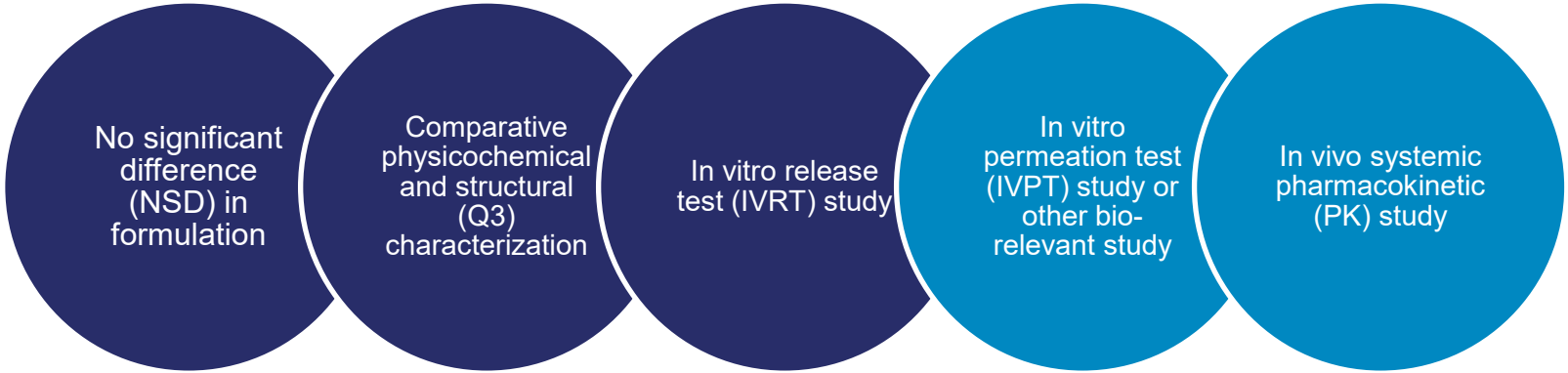
- Discuss your proposed concentrations or proposed formulation with the Agency early in product development, if needed

- Consult guidance for industry
  - Controlled Correspondence Related to Generic Drug Development
  - Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs
  - ANDA Submissions – Refuse-to-Receive Standards

MDE: Maximum Daily Exposure; IID: Inactive Ingredient Database

Characterization-Based BE Approach

In PSGs for topical products…



NSD Standard

- Built upon the principles for assessing Q1/Q2 sameness
- Also considers certain differences that have previously been determined to be acceptable based on available scientific evidence

To demonstrate bioequivalence for doxepin hydrochloride topical cream, 5% using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, 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.

- Does NOT mean that any formulation would be acceptable

Q1: Qualitative sameness; Q2: Quantitative sameness

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

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	12.00
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.

Feedback on Formulation: NSD Assessment

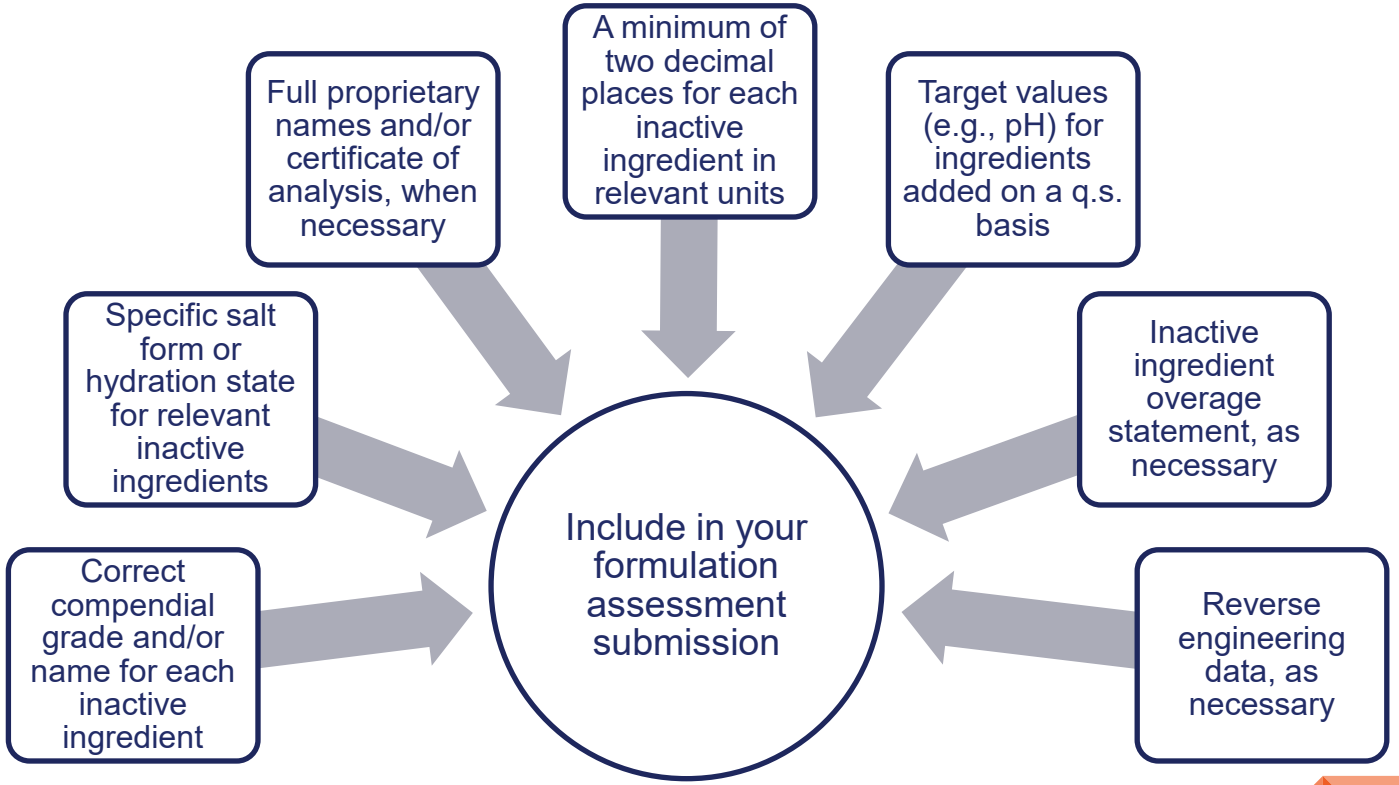
- Ask the correct question

  The question should ask whether one or more proposed formulation(s) may be suitable for the specific BE approach recommended in FDA's guidance.

- Include all necessary information related to formulation

  Information requests cause an extension of goal date.

Feedback on Formulation: NSD Assessment



Additional Considerations

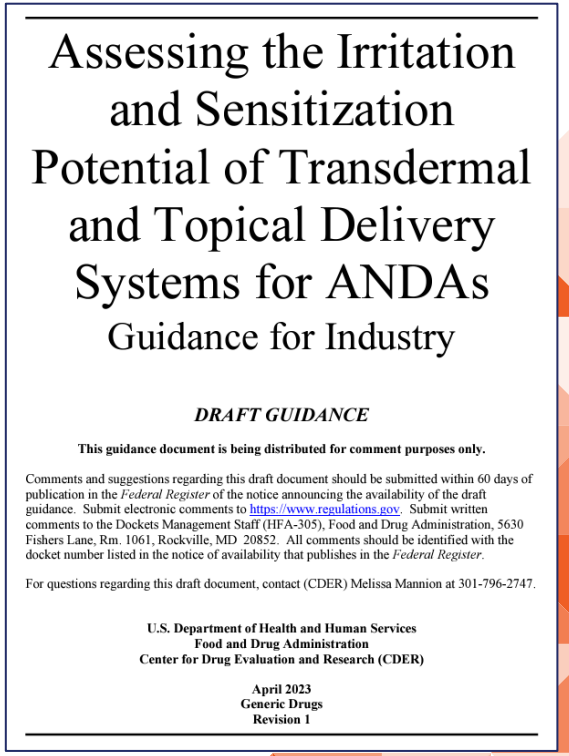
- Inactive ingredient (mixtures)
  - Clarify the components, composition, and manufacturing method (co-processed vs physical blend)
  - From Q1 perspective,

    E.g., separately added MCC and CMC ≠ co-processed MCC/CMC
- Compounding kit product
  - Provide formulation composition tables before and after admixing, each on 100% basis

MCC: microcrystalline cellulose; CMC: carboxymethylcellulose sodium

Feedback on Formulation: TDS Products

Active Ingredient:	Asenapine
Dosage Form; Route:	System; transdermal
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation and sensitization study



Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Melissa Mannion at 301-796-2747.

U.S. Department of Health and Human Services
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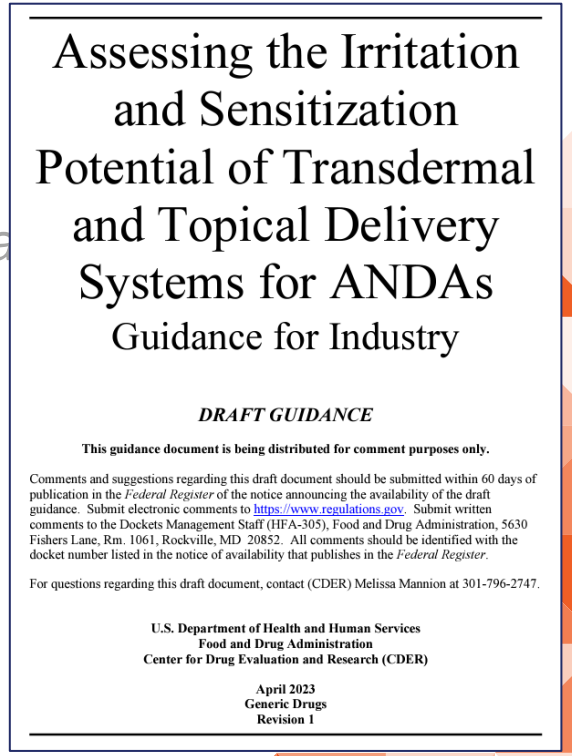
Generic Drugs
Revision 1

TDS: Transdermal/Topical delivery system

Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

Feedback on Formulation: TDS Products

In some circumstances, ***an in vivo sensitization evaluation of a TDS product may be unnecessary if adequate justification is provided*** *or FDA has determined that conducting a sensitization assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin sensitizer or based on information/data related to the components and composition of TDS product) to show that the T product is not likely to be more sensitizing than the R product.*



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Summary

- Engaging with the Agency through the CC program to gain feedback on formulation aspects throughout product development can be beneficial.

- Providing all essential information needed for the specific product and BE approach enhance efficiency in processing and assessment of the CC.

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Questions?

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