Current Recommendations and ANDA Landscape for Topical and Transdermal Delivery Systems (TDS)

Session 3: Using Research to Streamline Recommendations for TDS

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Advancing Generic Drug Development:
Modernizing Bioequivalence Approaches for Topical & Transdermal Products
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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Products covered
- Recommendations for establishing (bio)equivalence
- How GDUFA research was used to streamline recommendations
- Guidance evolvement and implementation
- Best practices for seeking FDA feedback

Products in Scope

Topical and Transdermal Delivery Systems (TDS)

- **Transdermal ER Film/System**
  - Asenapine
  - Buprenorphine
  - Clonidine
  - Dextroamphetamine
  - Donepezil Hydrochloride
  - Estradiol
  - Estradiol/Levonorgestrel
  - Estradiol/Norethindrone Acetate
  - Ethinyl Estradiol/Levonorgestrel
  - Ethinyl Estradiol/Norelgestromin
  - Fentanyl
  - Granisetron
  - Methylphenidate
  - Nicotine
  - Nitroglycerin
  - Oxybutynin
  - Rivastigmine
  - Rotigotine
  - Scopolamine
  - Selegiline
  - Testosterone
- **Topical System/Patch**
  - Capsaicin
  - Diclofenac Epolamine
  - Lidocaine
  - Lidocaine/Tetracaine
  - Menthol/Methyl Salicylate

Transdermal Semisolids

- **Gel**
  - Estradiol
  - Oxybutynin (Chloride)
  - Testosterone
- **Ointment**
  - Nitroglycerin

Transdermal Solutions

- **Solution/Spray**
  - Estradiol
  - Testosterone

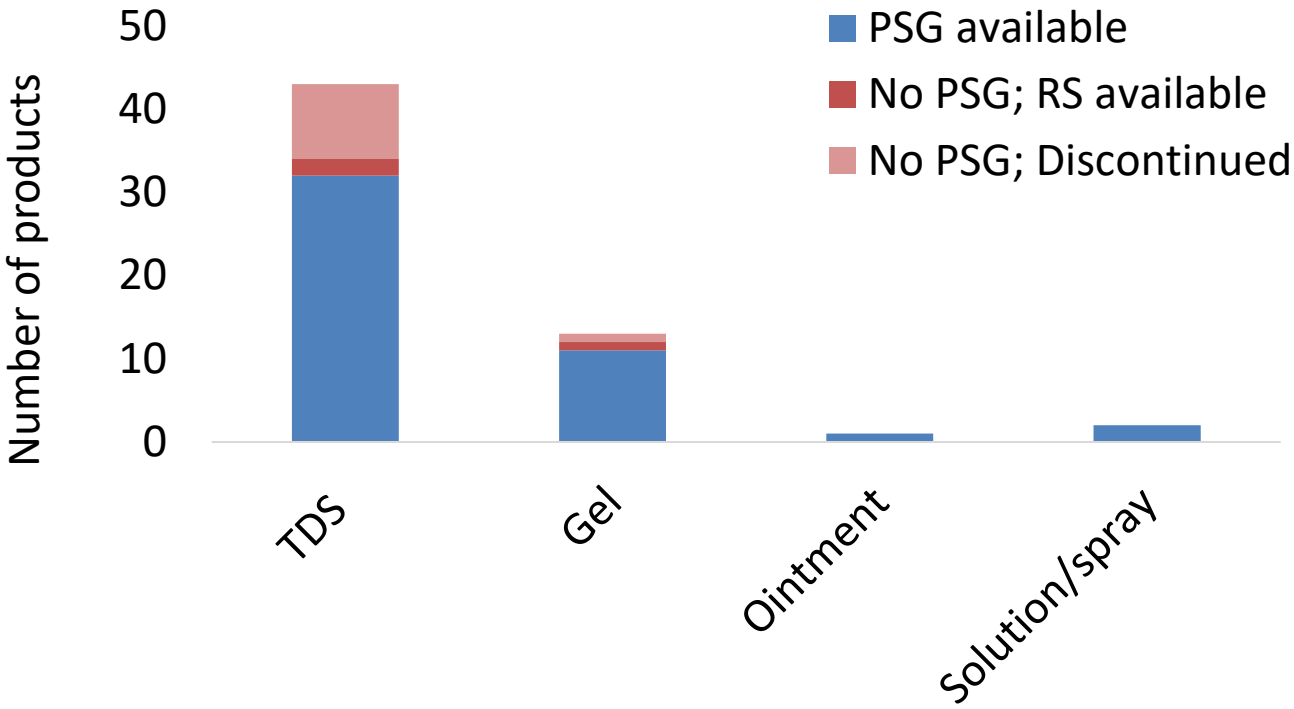
Data through Jun 22, 2026; Unique active ingredient only; ER: Extended Release

General PSG Recommendations

TDS	Gel
➢In Vivo BE Study with PK Endpoints ➢Adhesion Study ➢Skin Irritation Study (+ Sensitization Study) (I/S)	In Vivo BE Study with PK Endpoints
Ointment	**Solution/Spray**
In Vivo BE Study with PK Endpoints	21 CFR 320.22(b)(3) Waiver

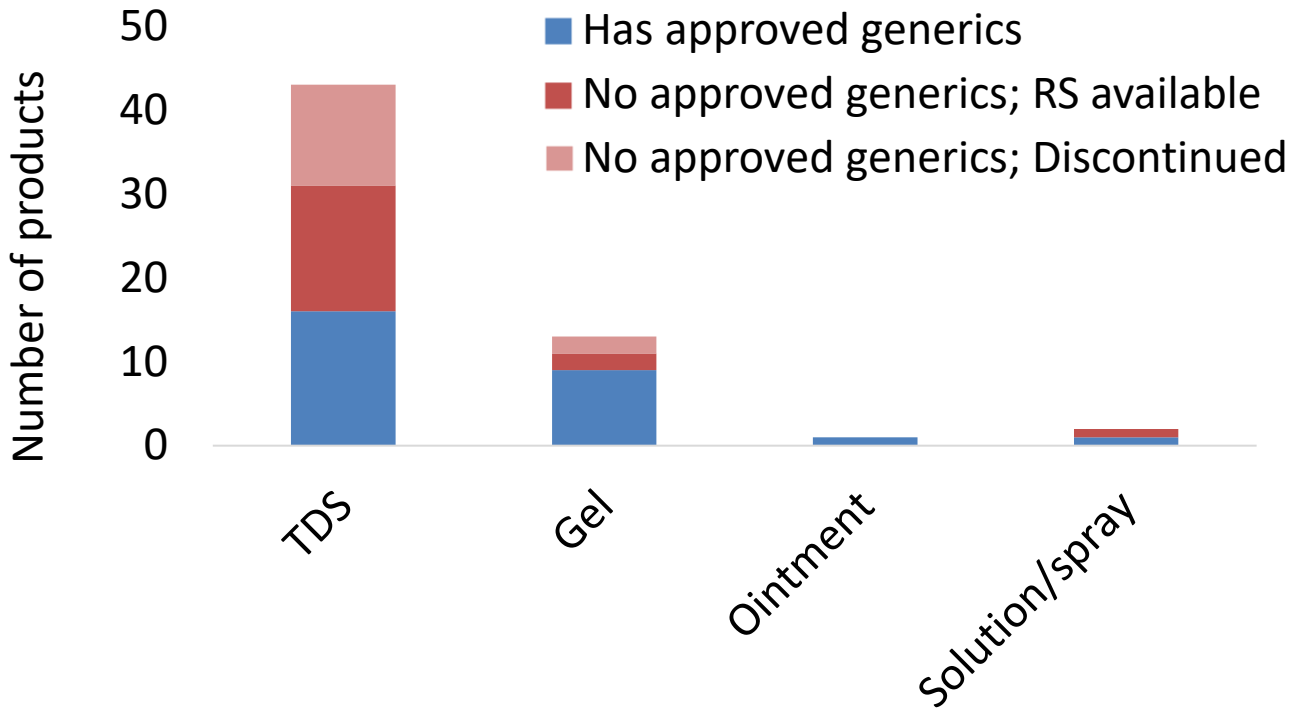
Data through Jun 22, 2026; BE: Bioequivalence; PK: Pharmacokinetic

PSG Coverage



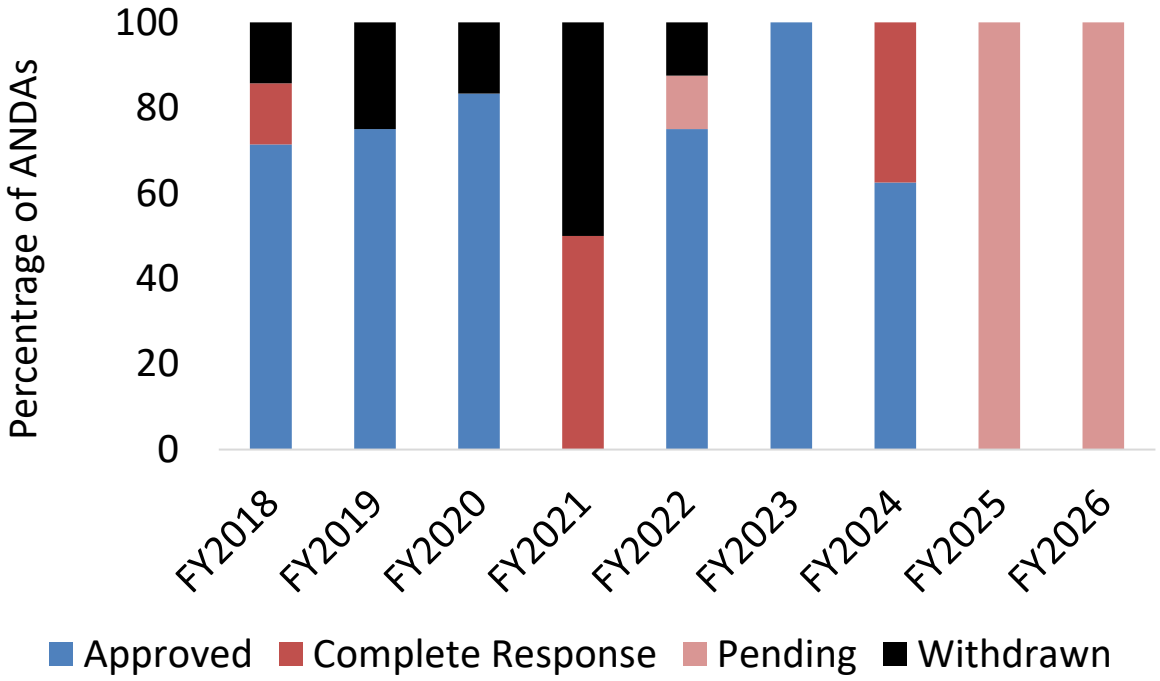
Data through Jun 22, 2026; RS: Reference Standard

Availability of Generics



Data through Jun 22, 2026.

ANDA Status

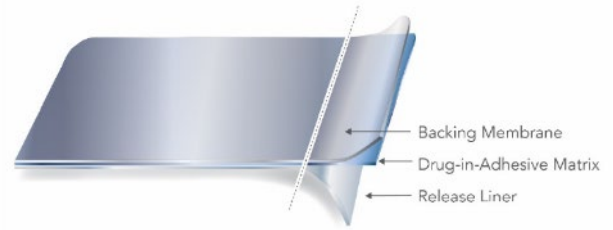


Data through Jun 22, 2026; Data were normalized by the number of ANDAs received within the same FY.

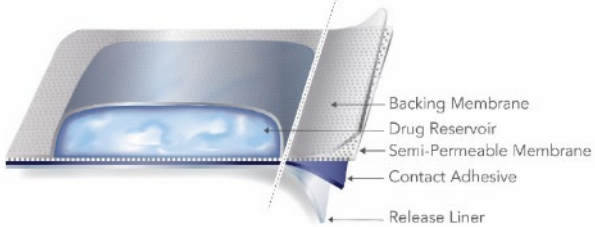
Research to Streamline I/S studies

Topical and Transdermal Delivery Systems, collectively TDS

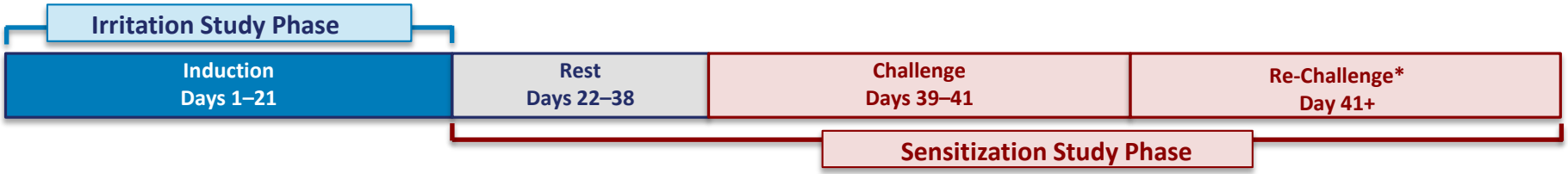
Matrix type system



Liquid or gel reservoir type system



Sensitization study (conducted in combination with skin irritation study) was a blanket recommendation for generic TDS.



** Re-Challenge conducted only if sensitization reactions observed at Challenge*

I/S: irritation and sensitization; Guidance for industry on *Transdermal and Topical delivery systems-product development and quality considerations* (Nov 2019)

Rationale for the Research

- Office of New Drugs no longer recommends standalone **studies designed solely to elicit/monitor contact dermatitis**.
- Skin sensitization studies can be a regulatory burden **(>200 subjects)**.
- Sensitization study subjects may **become sensitized** to a drug product or the components.
- Research Question
  - Can recommendations for I/S studies be streamlined for prospective generic TDS by analyzing the available data for approved products?

Guidance for Industry *Contact Dermatitis from Topical Drug Products for cutaneous Application: Human Safety Assessment* (March 2020)

Research Findings

RLD/RS used in the reviewed ANDA studies		ANDA Information		
RLD	API	Applications	Irritation failures	Sensitization failures
N021306	Buprenorphine	5	2	--
N018891	Clonidine	1	--	--
N020538	Estradiol	2	1	--
N203752	Estradiol	2	1	--
N021180	Ethinyl Estradiol; Norelgestromin	1	--	--
A200910	Ethinyl Estradiol; Norelgestromin	2	--	--
N019813	Fentanyl	1	--	--
N020612	Lidocaine	5	--	--
N021514	Methylphenidate	1	--	1
N021351	Oxybutinin	1	--	--
N022083	Rivastigmine	5	--	--
N017874	Scopolamine	4	--	--
Total		30	4	1

- No correlation between I/S failures and specific inactive ingredients.
- Sole sensitization failure attributed to API.
- Formulation, context of use, and databases (e.g., IID) may be leveraged when determining sensitization study needs for prospective TDS.

RLD: Reference Listed Drug; API: Active Pharmaceutical Ingredient; IID: Inactive Ingredient Database, Data between 10/01/2012-09/30/2022; Russo J et al. Poster Presentation at the American Academy of Dermatology 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024; FY2025 GDUFA Science and Research Report

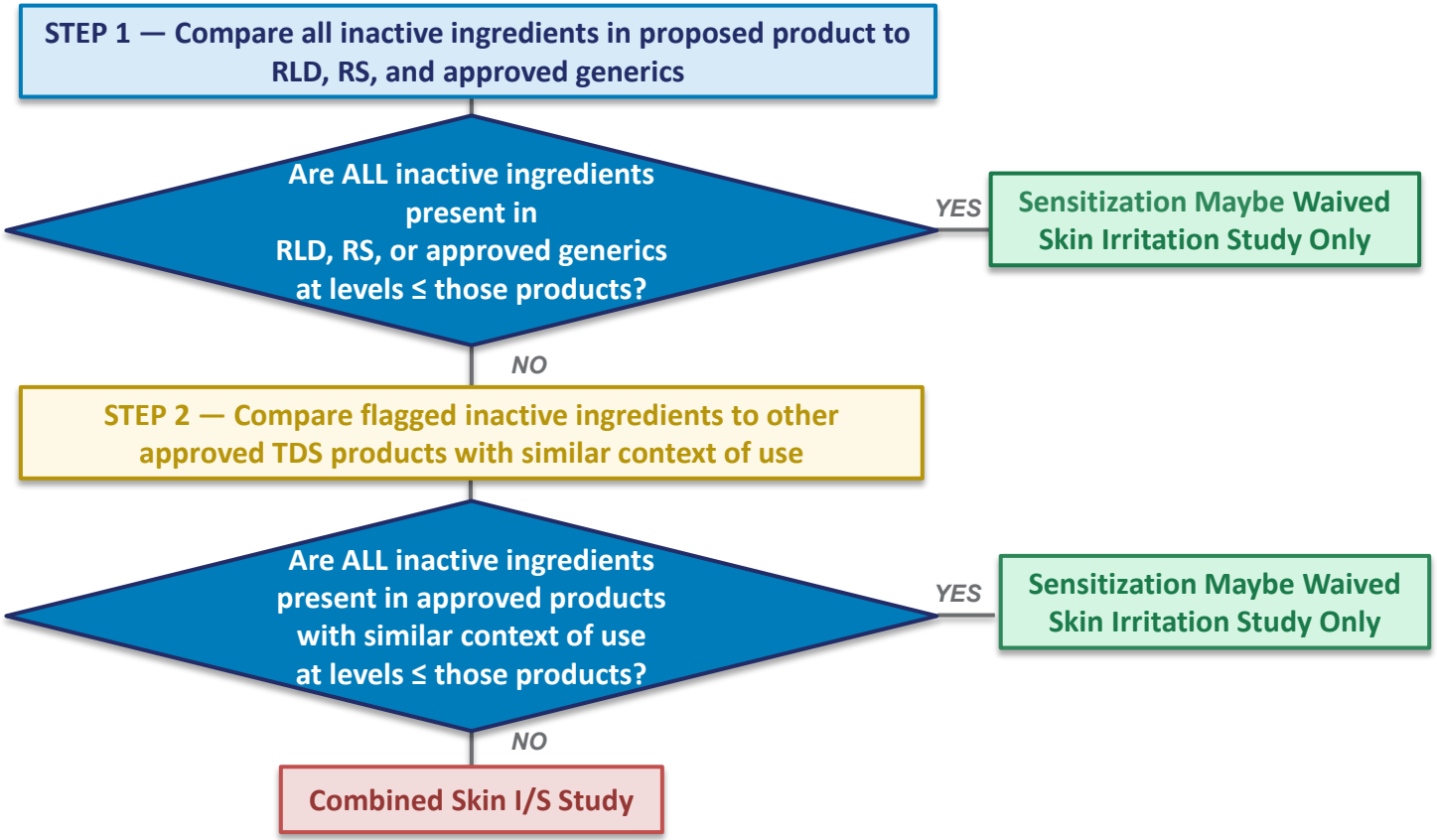
Guidance Evolvement

- **Apr 2024 I/S Guidance Revision:**
  - In some circumstances, an in vivo sensitization evaluation of a TDS product may be unnecessary if adequate justification is provided...

- **Feb 2026 PSG Batch Revision & July 2026 I/S Guidance Revision:**
  - **Skin irritation study** in a minimum of **40** evaluable subjects (sufficiently powered).
  - **Combined skin I/S study** only if the test product contains an inactive ingredient that is
    - not present in the RLD and is known to be sensitizing, or
    - at a higher amount/concentration than previously used in an FDA-approved drug product with a similar context of use.

PSG_212268 (February 2026) (representative PSG); Guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (April 2024 and July 2026)

Guidance Implementation



Example 1: Skin Irritation Study Recommended

Proposed test product 1

	Amount (mg/unit)	Concentration (%w/w)
Drug in adhesive matrix layer		
API	60	9
Adhesive X	420	66
Excipient 1	120	19
Excipient 2	40	6
Backing Film		
	Backing Film B	
Release Liner		
	Release Liner R	

MDE based on 1 x TDS;

Context of use: TDS for chronic use in pediatric patients

Disclaimer: Fictional products for illustration purpose only; MDE: Maximum Daily Exposure

Example 1: Skin Irritation Study Recommended

STEP 1: Compare All Inactive Ingredients to RLD, RS, Approved Generics

Amount (mg/unit)			
	Proposed test product	RLD/RS	Approved generics
Adhesive X	420	440	415
Excipient 1	120	125	110
Excipient 2	40	30	40

Concentration (%w/w)			
	Proposed test product	RLD/RS	Approved generics
Adhesive X	66	67	65
Excipient 1	19	19	18
Excipient 2	6	5	6

	Proposed test product	RLD/RS	Approved generics
Backing Film	Backing Film B	Backing Film F	Backing Film B

Skin Irritation Study Only

Disclaimer: Fictional products for illustration purpose only

Example 2: Combined I/S Study Recommended

Proposed test product 2

	Amount (mg/unit)	Concentration (%w/w)
Drug in adhesive matrix layer		
API	60	9
Adhesive X	420	66
Excipient 1	120	19
Excipient 3	40	6
Backing Film		
	Backing Film B	
Release Liner		
	Release Liner R	

Compared to proposed test product 1, same RLD; Only difference is Excipient 2 → Excipient 3.

Disclaimer: Fictional products for illustration purpose only

Example 2: Combined I/S Study Recommended

STEP 1: Compare All Inactive Ingredients to RLD, RS, Approved Generics

Amount (mg/unit)			
	Proposed test product	RLD/RS	Approved generics
Adhesive X	420	440	415
Excipient 1	120	125	110
Excipient 3	**40**	**Not present**	

Concentration (%w/w)			
	Proposed test product	RLD/RS	Approved generics
Adhesive X	**66**	67	65
Excipient 1	**19**	19	18
Excipient 3	**6**	**Not present**	

	Proposed test product	RLD/RS	Approved generic
Backing Film	Backing Film B	Backing Film F	**Backing Film B**

Proceed to STEP 2

Disclaimer: Fictional products for illustration purpose only

Example 2: Combined I/S Study Recommended

STEP 2: Compare flagged ingredients to other approved TDS with similar context of use

	Amount (mg/unit) or MDE (mg)		Similar context of use?
	Proposed test product	Equal or Higher level	
Excipient 3	40	42 in Product A	No, acute use in adults

Combined Skin I/S Study

	Concentration (%w/w)		Similar context of use?
	Proposed test product	Equal or Higher level	
Excipient 3	6	7 in Product B	Yes

Disclaimer: Fictional products for illustration purpose only

Best Practices for Seeking FDA Feedback

Requesting feedback on prospective formulation

- Submit CC or PDEV meeting request as appropriate
- Submit complete formulation information:
  - All components in all layers
  - Mg/unit and %w/w (except for films and liners)
  - Full trade name, COA, DMF number as available
  - TDS structural design, size, and proportionality
- Seek feedback before conducting any in vivo study

Requesting feedback on alternative approach for semisolids/solutions

CC: Controlled Correspondence; PDEV: Product Development; COA: Certificate of Analysis; DMF: Drug Master File

Summary

- Broad PSG coverage and robust ANDA pipeline reflect continued progress in advancing generic product development for TDS and other transdermal products.
- GDUFA Research supported a shift from blanket sensitization recommendations to a risk-based approach and smaller sample size for skin irritation only studies.
- Recent guidance updates (Feb & July 2026) can significantly reduce regulatory burden and support the development of TDS products.
- If questions arise related to the formulation, engagement with FDA is strongly encouraged prior to conducting any in vivo studies.

GDUFA: Generic Drug User Fee Amendments

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  - Office of Pharmaceutical Quality Assessment
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- Office of New Drugs
  - Hon Sum Ko, MD

Resources

Guidances:

- Draft guidance for industry: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (July 2026)
- Final Guidance for industry: *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (May 2026)
- Final Guidance for industry: *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* (July 2026)
- Draft Guidance for industry: *Transdermal and Topical delivery systems-product development and quality considerations* (Nov 2019)
- Final Guidance for industry: *Residual Drug in Transdermal and Related Drug Delivery Systems (August 2011)*
- Final guidance for industry: *Controlled Correspondence Related to Generic Drug Development* (March 2024)
- Final guidance for industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

Websites:

- Product-Specific Guidances for Generic Drug Development website
- Upcoming Product-Specific Guidances for Generic Drug Product Development website
- Generic Drugs Science & Research Program

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Questions?

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