

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
September 10, 2026



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 evolution and implementation
- Best practices for seeking FDA feedback

Products in Scope

Topical and Transdermal Delivery Systems (TDS)

- | | |
|---|--|
| <ul style="list-style-type: none"> • Transdermal ER Film/System | <ul style="list-style-type: none"> Nicotine Nitroglycerin Oxybutynin Rivastigmine Rotigotine Scopolamine Selegiline Testosterone |
| <ul style="list-style-type: none"> Asenapine Buprenorphine Clonidine Dextroamphetamine Donepezil Hydrochloride Estradiol Estradiol/Levonorgestrel Estradiol/Norethindrone Acetate Ethinyl Estradiol/Levonorgestrel Ethinyl Estradiol/Norelgestromin Fentanyl Granisetron Methylphenidate | <ul style="list-style-type: none"> • Topical System/Patch |
| | <ul style="list-style-type: none"> Capsaicin Diclofenac Epolamine Lidocaine Lidocaine/Tetracaine Menthol/Methyl Salicylate |

Transdermal Semisolids

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

Transdermal Solutions

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

General PSG Recommendations

TDS

- In Vivo BE Study with PK Endpoints
- Adhesion Study
- Skin Irritation Study (+ Sensitization Study) (I/S)

Gel

In Vivo BE Study with PK Endpoints

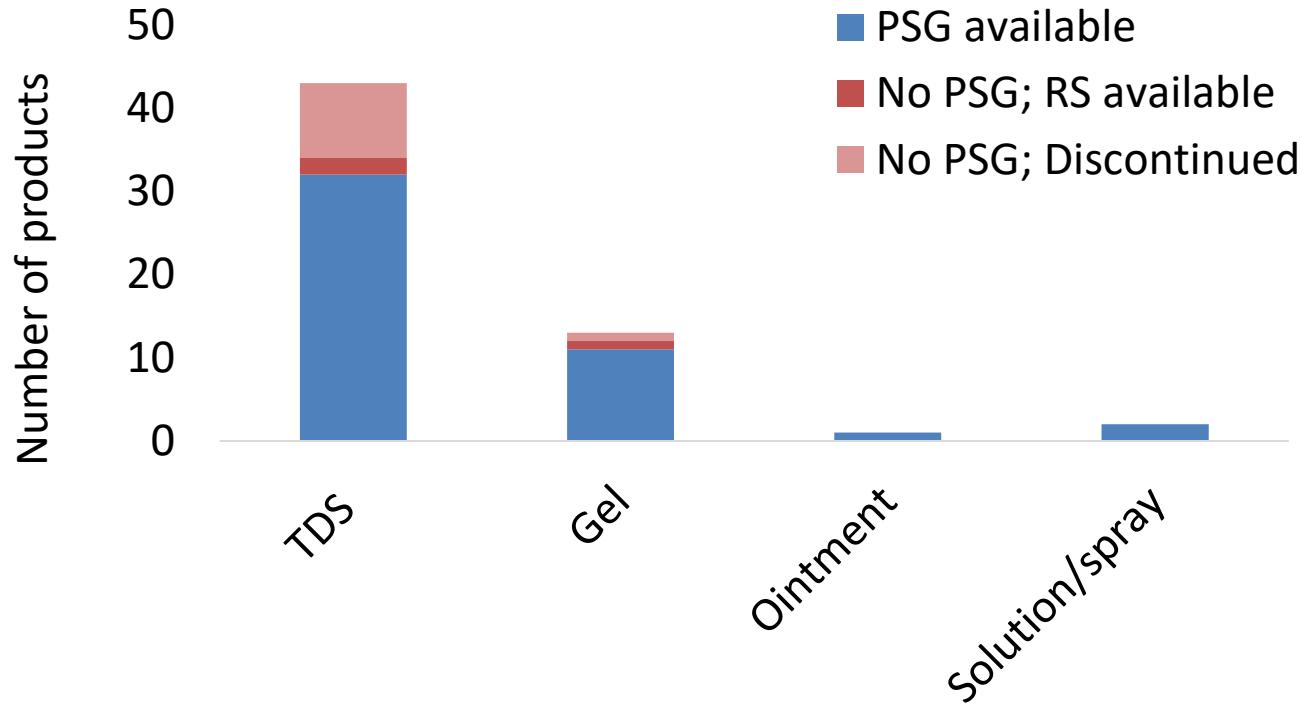
Ointment

In Vivo BE Study with PK Endpoints

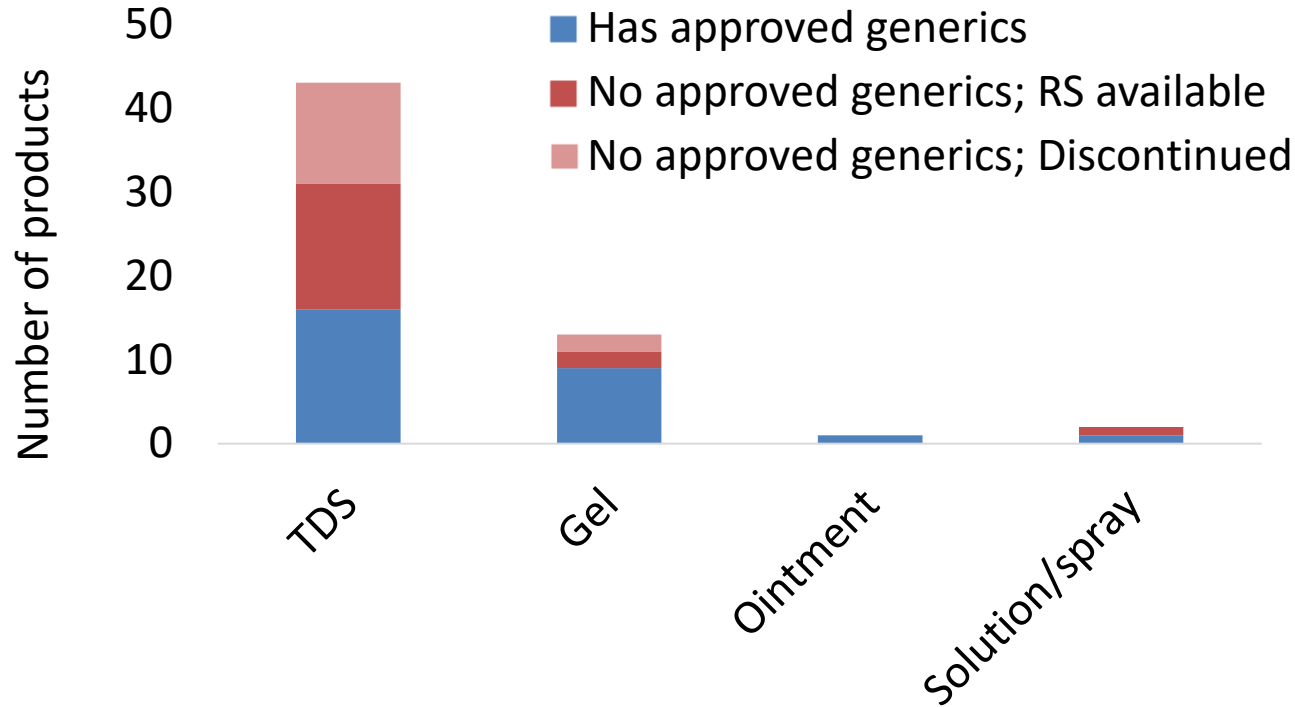
Solution/Spray

21 CFR 320.22(b)(3) Waiver

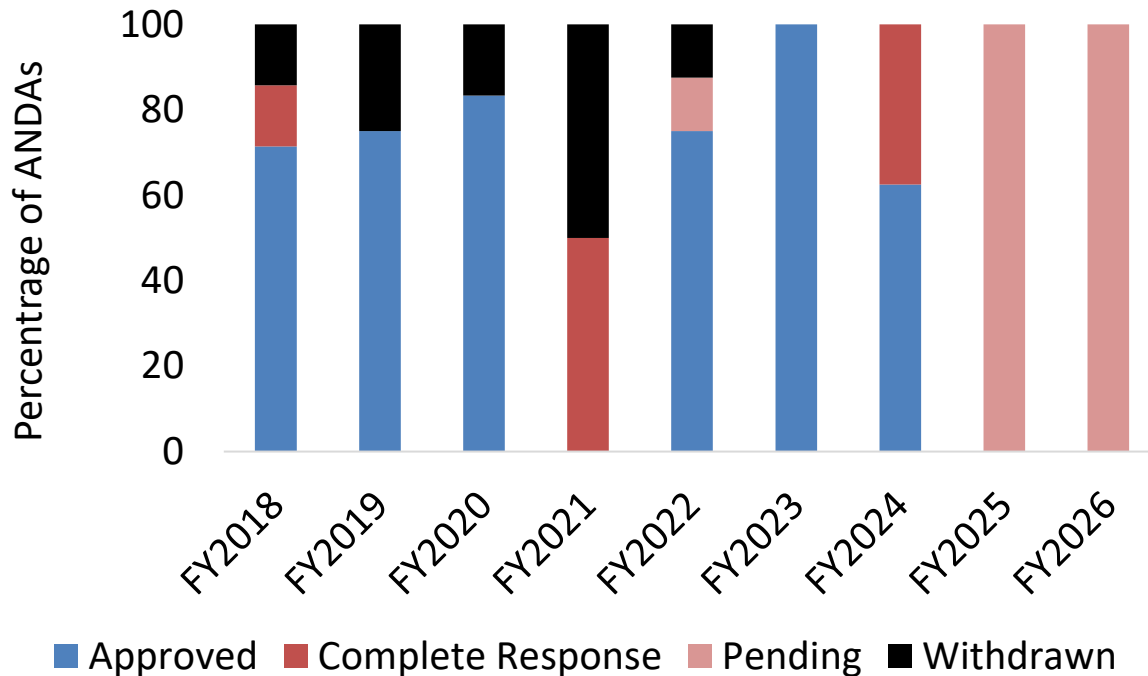
PSG Coverage



Availability of Generics

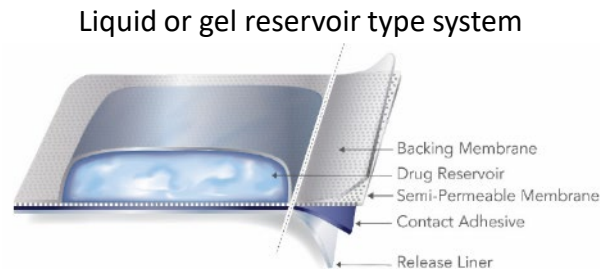
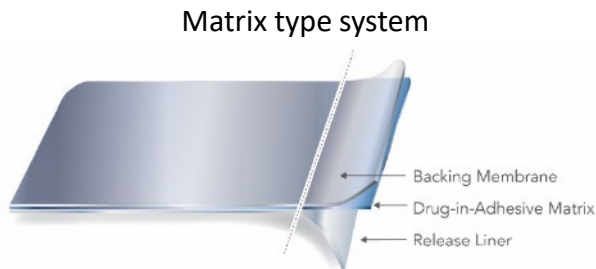


ANDA Status

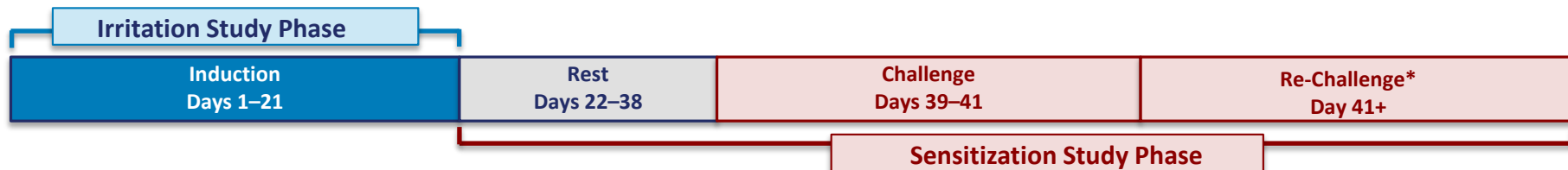


Research to Streamline I/S studies

Topical and Transdermal Delivery Systems, collectively TDS



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

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?



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

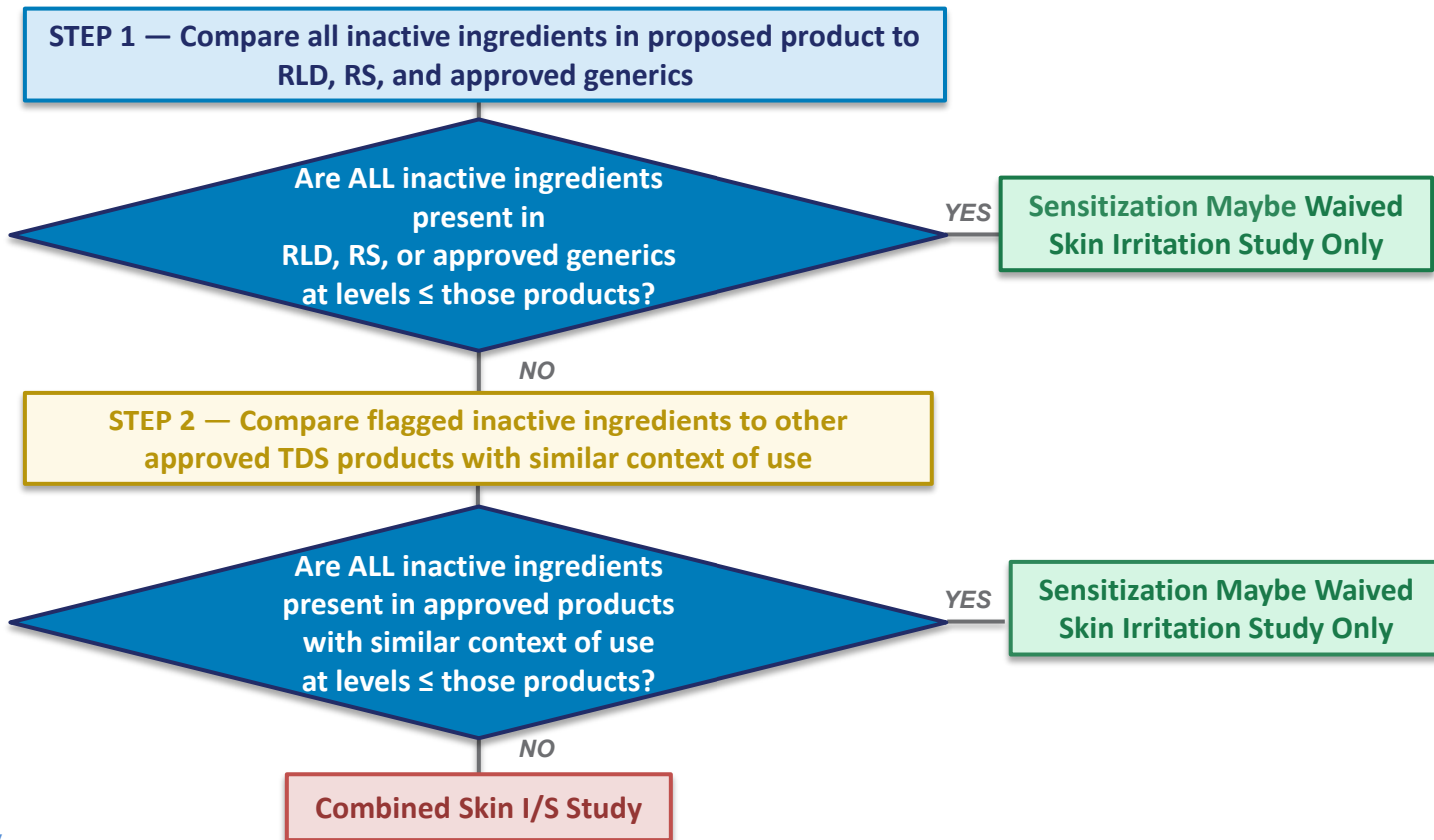
- No correlation between I/S failures and specific inactive ingredients.
- Sole sensitization failure attributed to API.
- Formulation, context of use, and databases (e.g., IID) may be leveraged when determining sensitization study needs for prospective TDS.

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.

Guidance Evolvment

- **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.

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

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

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.

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

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



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

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.

Acknowledgements

- Office of Generic Drugs
 - Office of Research and Standards
 - Jackson Russo, PhD (Former ORISE Fellow)
 - Priyanka Ghosh, PhD
 - Megan Kelchen, PhD
 - Tannaz Ramezanli, PharmD, PhD
 - Markham Luke, MD, PhD
 - Sam Raney, PhD
 - Robert Lionberger, PhD
 - John Nguyen, PharmD
 - Andrew Clerman, MD, PhD (now OND)
 - Jihong Shon, MD
 - Myong Jin Kim, PharmD
 - Mirette Mina, PharmD
 - Joseph Kotsybar, PharmD
 - Office of Safety and Clinical Evaluation
 - Mitchell Frost, MD
 - Lisa Faulcon, MD
 - Ying Fan, PhD
 - Christina Streets, PhD
 - Office of Bioequivalence
 - Bing Li, PhD
 - Office of Generic Drug Policy
- Office of Translational Sciences
 - Office of Biostatistics
 - Wanjie Sun, PhD
 - Somesh Chattopadhyay, PhD
 - Fairouz Makhoul, PhD
 - Stella Grosser, PhD
- Office of Pharmaceutical Quality
 - Office of Pharmaceutical Quality Assessment
 - Robert Berendt, PhD
 - Caroline Strasinger, PhD
- 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](#)

Questions?

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