Bioequivalence of Transdermal Delivery Systems – Scientific Merits of the U.S. Approach

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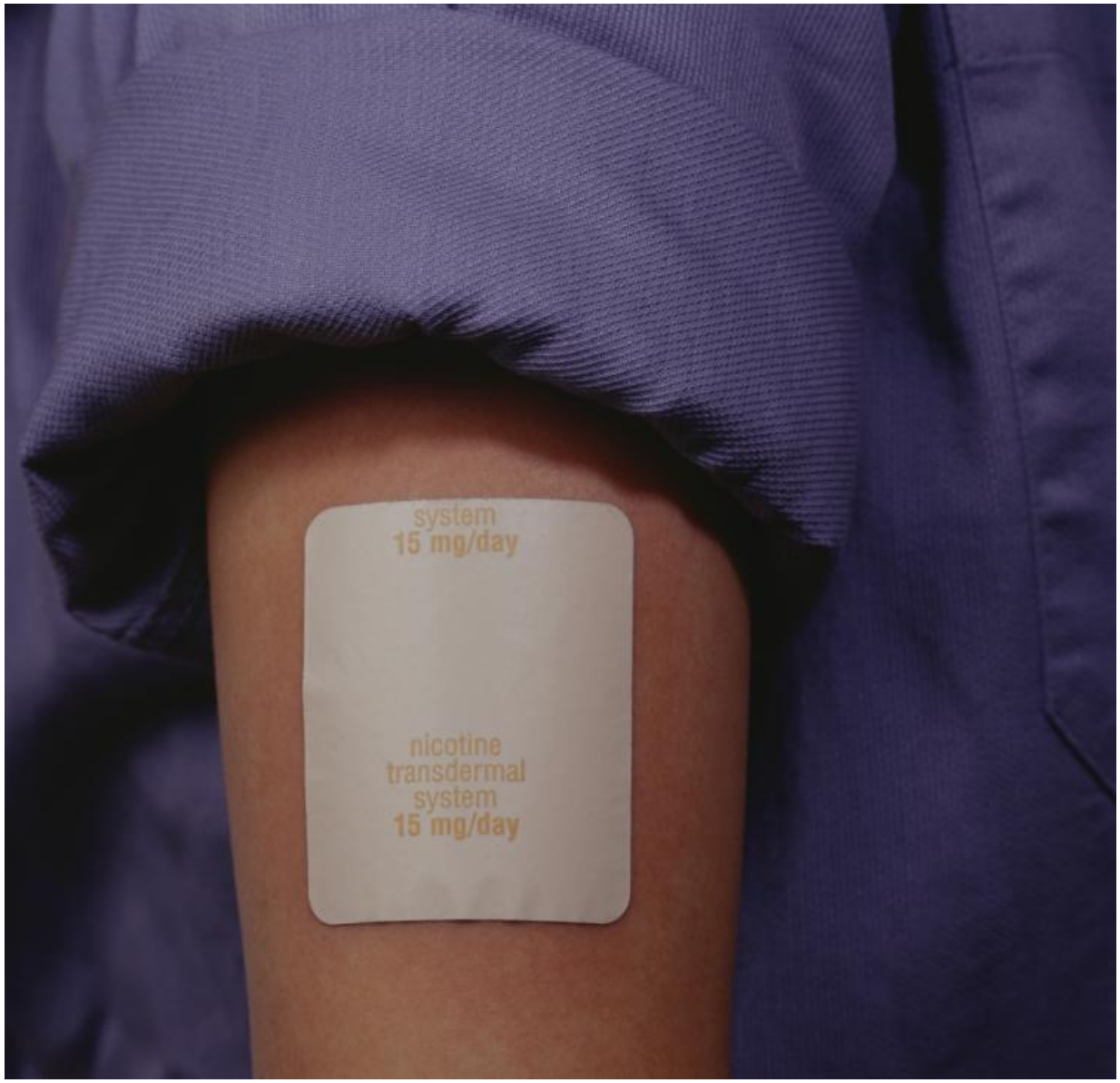
The Global Bioequivalence Harmonisation Initiative

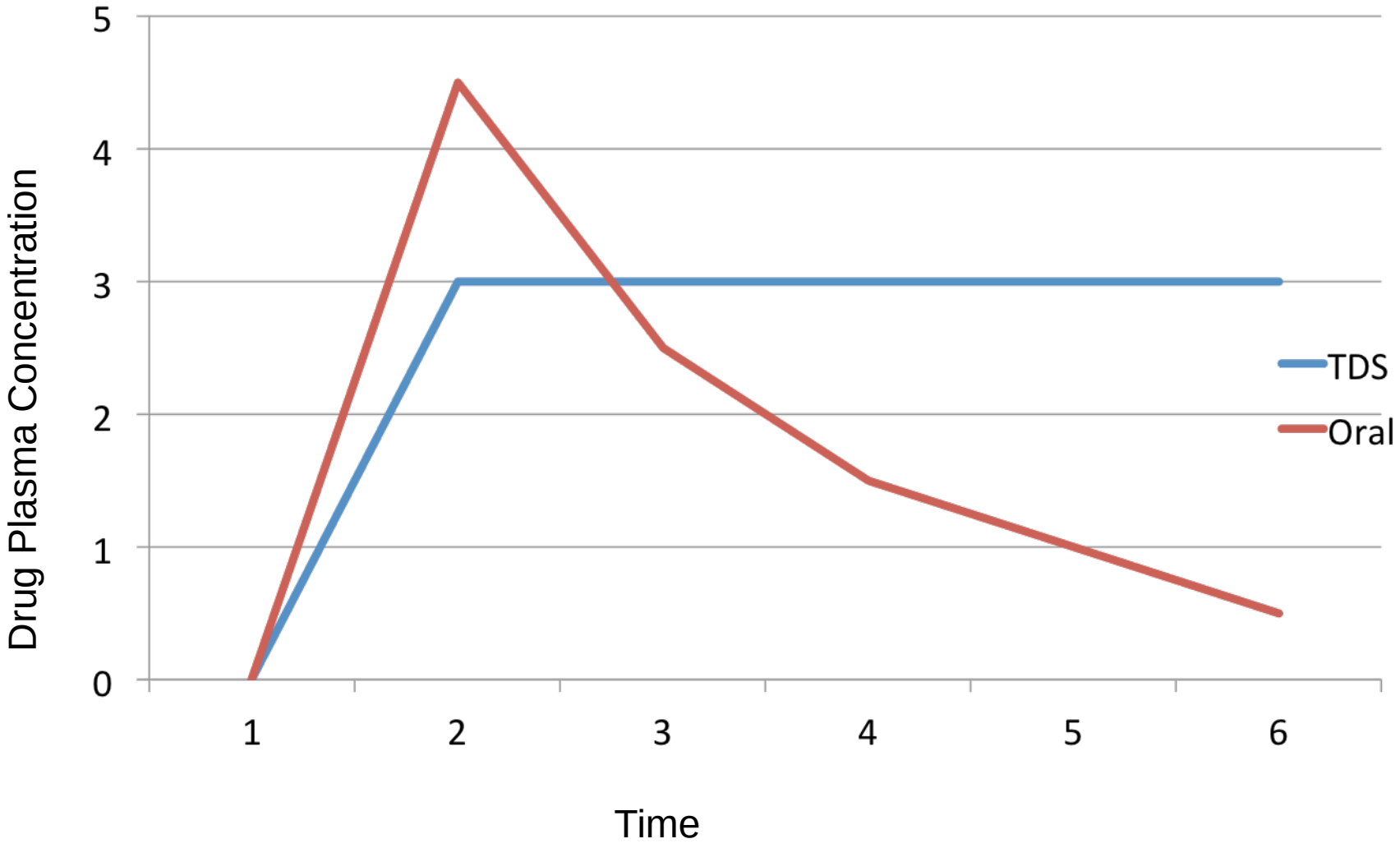

system
15 mg/day
nicotine
transdermal
system
15 mg/day

Transdermal delivery systems

Are dosage forms that, when applied to intact skin, are designed to deliver drugs to the systemic circulation.

Are combination drug/device products with a primary mode of action of drug

PK – TDS vs. Oral



Transdermal delivery systems

- Generally designed to deliver drug at a constant rate to achieve steady-state blood concentration and maintained until the patch is removed.
- How do we define product activity?
  - The **release rate** of the drug from the patch
  - The **total duration** of the drug release
  - The patch surface area, drug concentration, skin API penetration, membrane/solvent flux can all affect activity profile.

General BE Regulatory Principles

- Therapeutic Equivalence
  - Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent to their RLD
  - TE = BE + PE
    - Products classified as therapeutically equivalent can be expected to produce the same clinical effect and safety profile as the RLD under conditions specified in labeling
  - Same expectation for generic drug-device combination products

- Applicants should generally seek approval of a presentation approved for the RLD
  - However, FDA does not expect that a generic drug-device combination product and its RLD need to be IDENTICAL in all respects
- Considerations
  - Performance characteristics
  - User Interface

US FDA guidance documents

Two general guidances:

2011 final guidance - Residual drug in transdermal and related drug delivery systems

2016 draft guidance - Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

Multiple Product Specific Guidances (PSGs)

Currently available PSG's for TDS

Transdermal delivery systems	Topical delivery systems (patches)
Buprenorphine	Diclofenac epolamine
Clonidine	Lidocaine
Estradiol (4 PSG's for 4 RS)	Menthol, methyl salicylate
Ethynil estradiol, norelgestromin	
Fentanyl	
Granisetron	
Methylphenidate	
Nicotine	
Nitroglycerin (2 PSG's for 2 RS)	
Oxybutynin (2 PSG's for 2 RS)	
Rivastigmine	
Rotigotine	
Scopolamine	
Selegiline	
Testosterone	

Product Specific Guidances

- PSGs allow for a tailored approach for developing a generic for each drug product
- Example – Buprenorphine Film, ER, transdermal
  - Three studies are recommended
    1) BE with PK Endpoints (single dose) – discusses utilizing naltrexone block and dosage strength – 20 mcg/hr for 7 days – analyte is buprenorphine in plasma 90% CI.
    2) Adhesion Study – single dose, two-treatment, two period crossover – again with naltrexone block
    3) Skin Irritation and Sensitization Study – Randomized, evaluator-blinded, in vivo within-subject repeat test – discusses use of vehicle only patch and study conduct

Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

Draft 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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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) Kris Andre at 240-402-7959.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Generic Drugs

Reason for Adhesion Evaluation

1) The amount of drug delivered into and thru the skin with a TDS is dependent, in part, on the surface area dosed.

2) The surface area dosed depends on the contact surface area being maintained throughout the duration of wear of the TDS.

3) Loss of adherence may result in reduced drug delivered to the patient

U.S. Sticking Principles

- During the course of the product's labeled wear, a TDS will encounter torsional strains arising from movement, changes in environmental temperature or humidity – e.g. due to contact with water or perspiration, and contact with clothing, other surfaces.
- Varying degrees of TDS detachment, including complete detachment can occur during wear.

Adhesion Scoring System

For each assessment, use a 5-point scale where each score corresponds to a specified range of adhered TDS surface area:

0 = ≥90% adhered (essentially no lift off the skin)

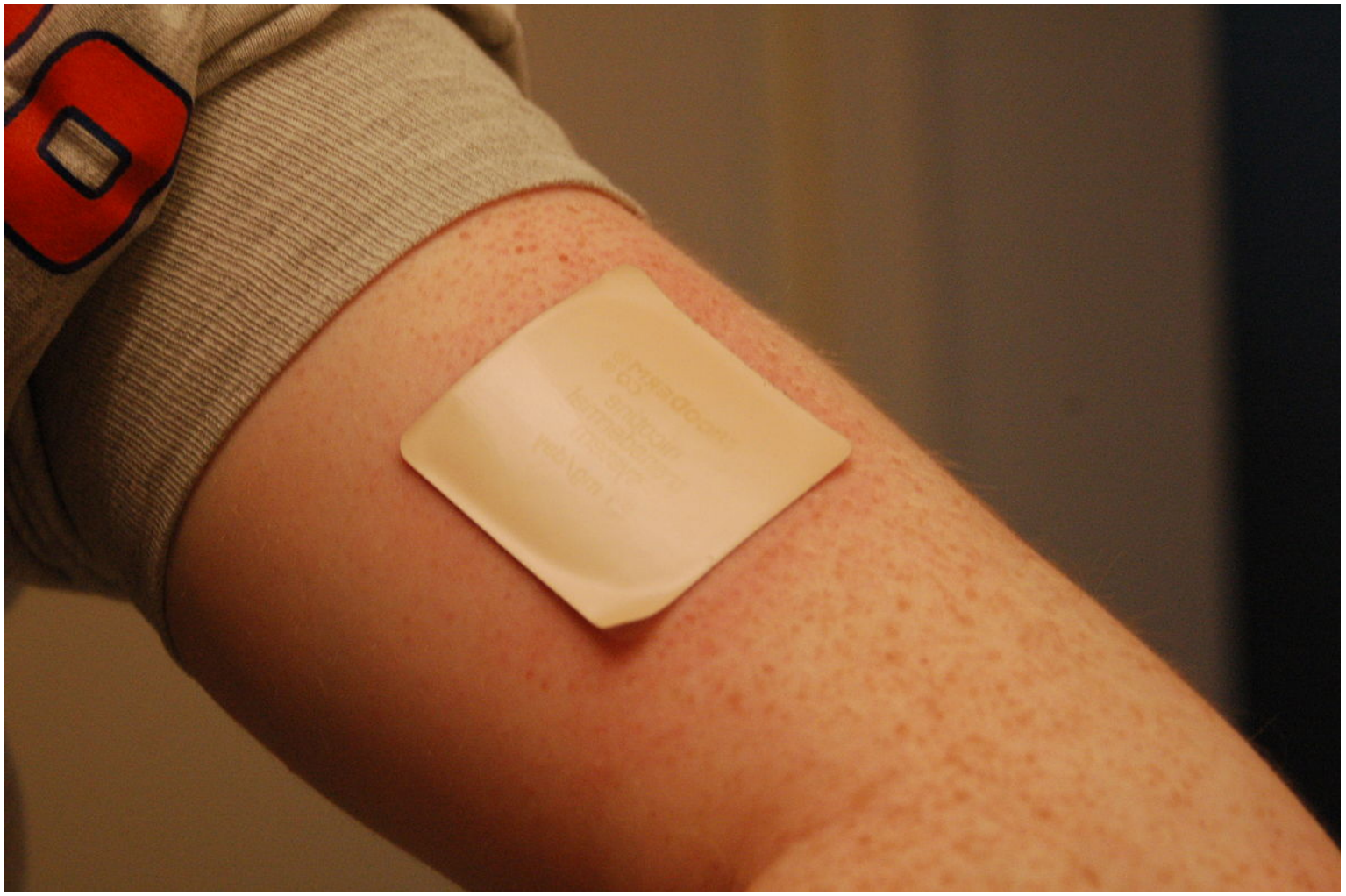
1 = ≥75% to <90% adhered (some edges only lifting off the skin)

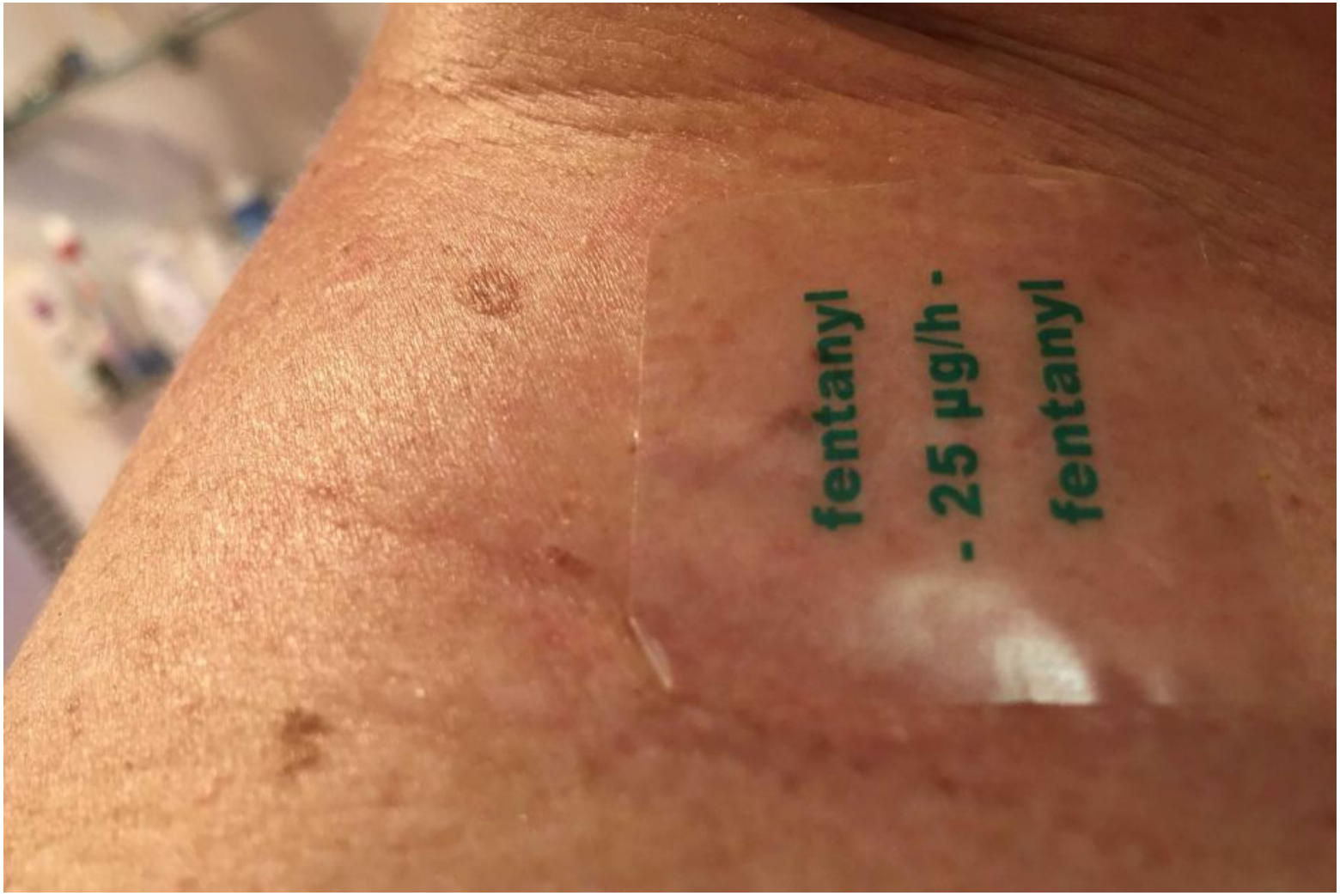
2 = ≥50% to <75% adhered (less than half of the TDS lifting off the skin)

3 = >0% to <50% adhered (not detached, but more than half of the TDS lifting off the skin, without falling off)

4 = 0% adhered (TDS detached; completely off the skin)

With each consecutive assessment, the highest adhesion score (representing the greatest degree of TDS detachment) assessed at any time point should be used for subsequent time points until a higher score is assessed. For a TDS that completely detaches, a score of 4 should be assigned for all remaining assessments scheduled for that TDS across the study duration.




fentanyl
- 25 µg/h -
fentanyl

Statistical Matters

- Sun, Grosser, Kim, and Raney explored the statistical ramifications of the new adhesion guidance as well as comparing the new U.S. approach to that outlined in the EMA 2015 “Guideline on quality of transdermal patches”.
- FDA’s 5-point scale may not estimate adhesion as precisely as EMA approach

Statistics Matter

- However, the EMA's primary endpoint may not discriminate two TDS products that have comparable adhesion at the last assessment, but different temporal profiles of adhesion performance (e.g. early vs. late detachment)
- EMA approach may not discriminate when adhesion scores improve across assessments due to intentional or unintentional manipulation (e.g. applying pressure on TDS)

Skin Irritation and Sensitization

- Sometimes done with vehicle only patch if drug has safety concerns
- Irritation and sensitization can be combined in a single study.
- Need to show that the rate of sensitization (irritation) to test patch is no worse than the rate of sensitization (irritation) with RLD.

Recommended Study*

- 21 day Induction Phase – sequential patch application every x number of days for a total of 21 consecutive days.
- 14 to 17 day rest period
- 48 hour Challenge Phase – Dermal response and other effects evaluated at 30 minute, 24, 48, and 72 hours after Challenge.
- At least 200 evaluable subjects in PP population

* Current recommendations, as spelled out in FDA product specific guidances for TDS products. No general guidance on Irritation or Sensitization Studies at this time.

Dermal Irritation Response Scale

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Current FDA TDS Research

FIGURE SOURCES: © http://www.clinicaladvisor.com/termsandconditions/ (Authorized non-commercial use)
Inset image from the Ortho Evra® Prescribing Information (package insert)

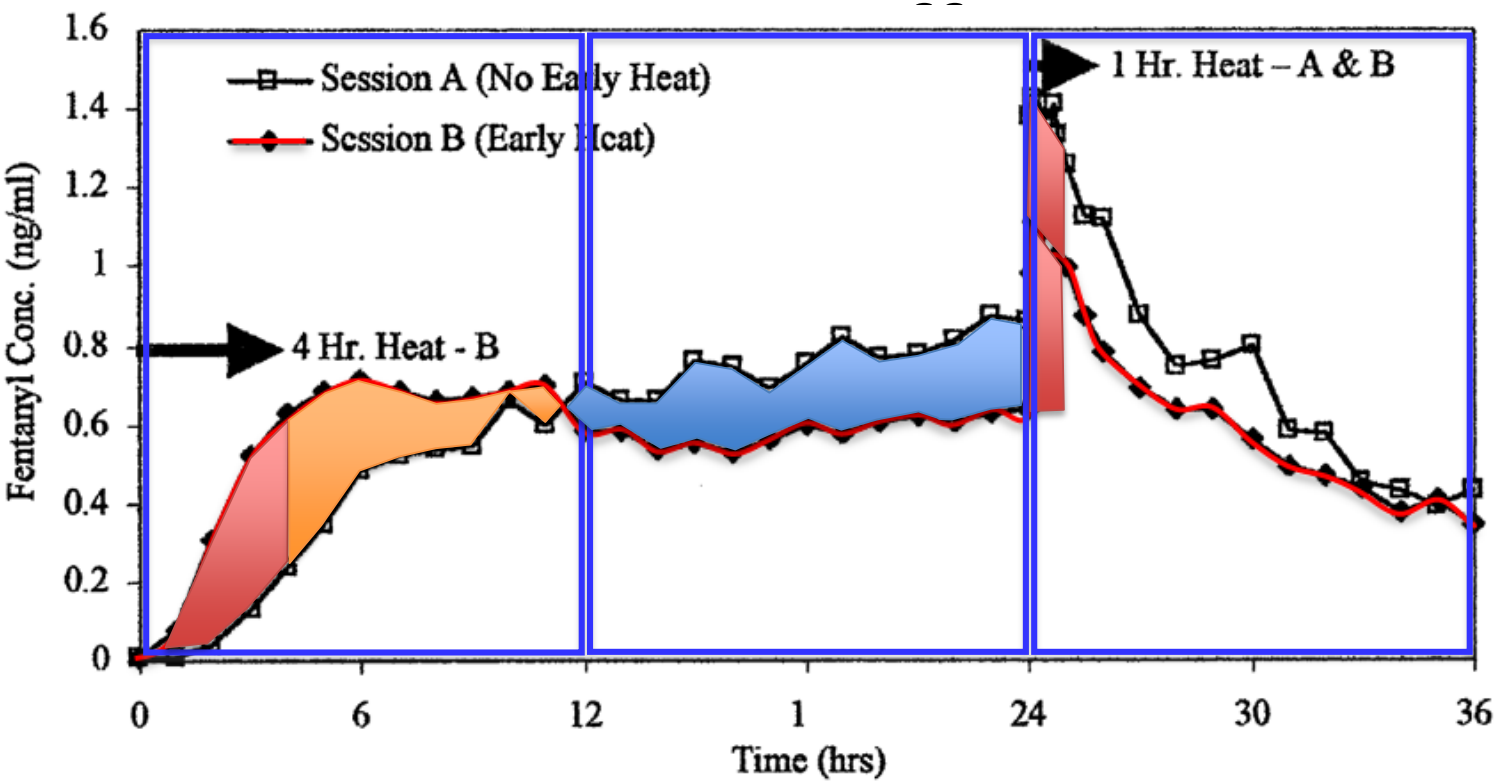


Figure 1. Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

FIGURE SOURCE: Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. Journal of Pain Vol. 4, No 6: 291-297

Questions about EU approach

- Are there different use paradigms between US and EU that might call for different approaches?
- Why have a multidose approach (See EMA Guideline)? What purpose does it serve?
- Regarding standards and excipient lists – how relevant are those to TDS?
- Do excipient lists indicate maximum amount to be included – especially with regard to allergens and potential toxins?

Concluding Comments

- The U.S. regulatory approach to Trans-Dermal Systems (TDS) is evolving
- We continue to explore new approaches to evaluating bioequivalence and quality for these products.
- We continue to examine what issues are most necessary (such as adhesion) and what issues may not be as necessary in evaluating these products.

Thank you

Special thanks to:
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Questions?

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