Development of CGDPs involving a Transdermal Delivery System (TDS)

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Session Description and Objectives

This presentation will utilize case studies to illustrate how to efficiently navigate product development for TDS products, discuss the specific in vitro and in vivo studies that are recommended to support a demonstration of BE for prospective generic TDS products, and clarify unique product quality issues impacting certain types of TDS products.

- Describe and explain the scientific considerations relevant to BE for TDS products.
- Describe, explain, clarify and/or discuss FDA's recommendations and relevant Guidance documents related to TDS products.
- Determine which of the available formats (controlled correspondences, pre-ANDA meeting requests, etc.) would be the appropriate one via which to request FDA's recommendations and feedback for different types of questions related to the development of complex generic TDS products.

Biography and Contact Information

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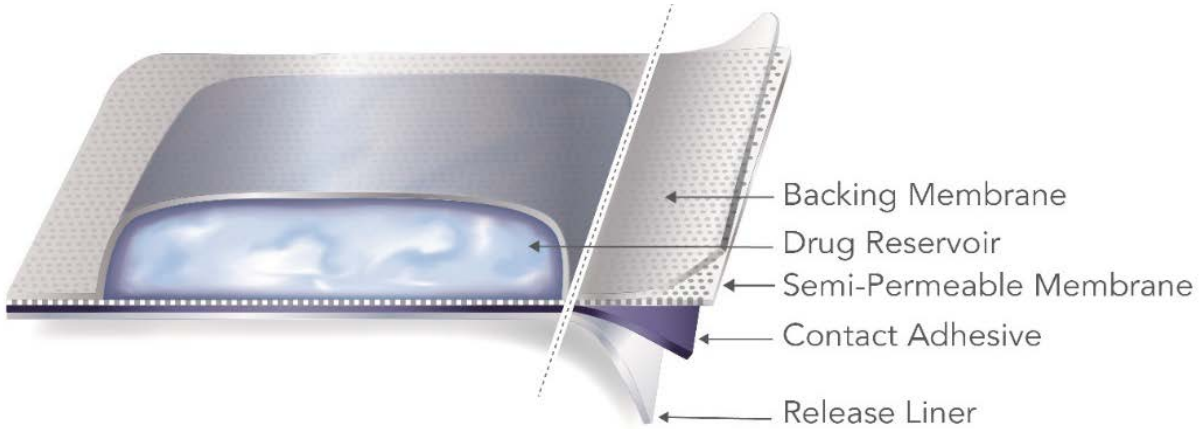
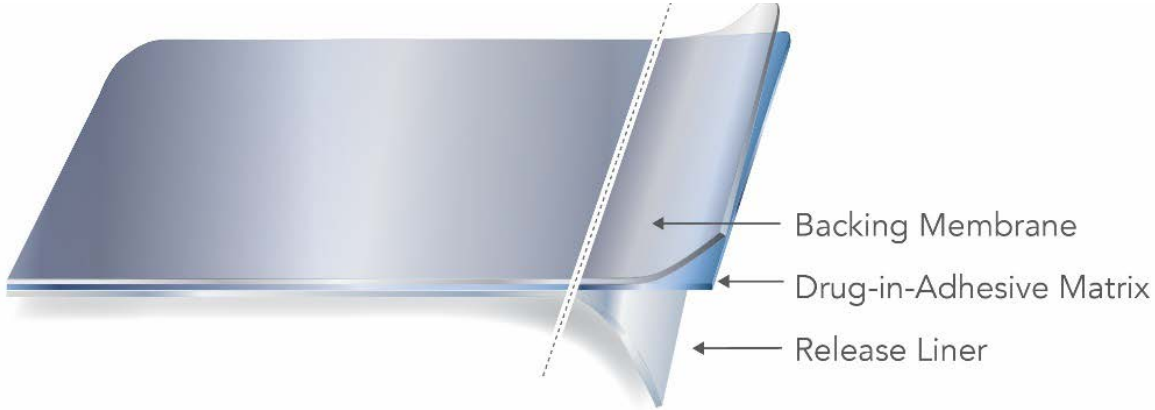
Transdermal Delivery Systems (TDS)

Reservoir TDS



Matrix TDS

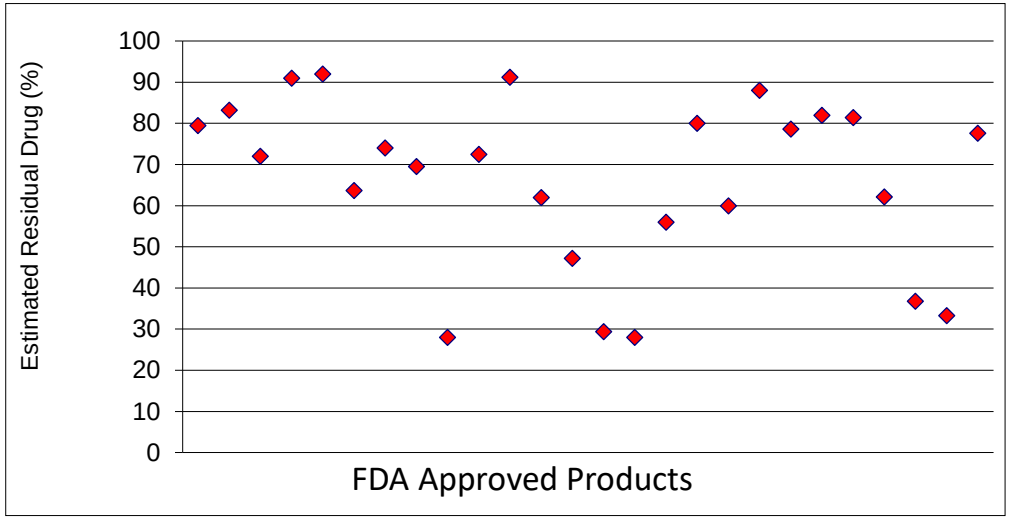


TDS Design Considerations: Residual Drug

FDA Residual Drug Guidance:

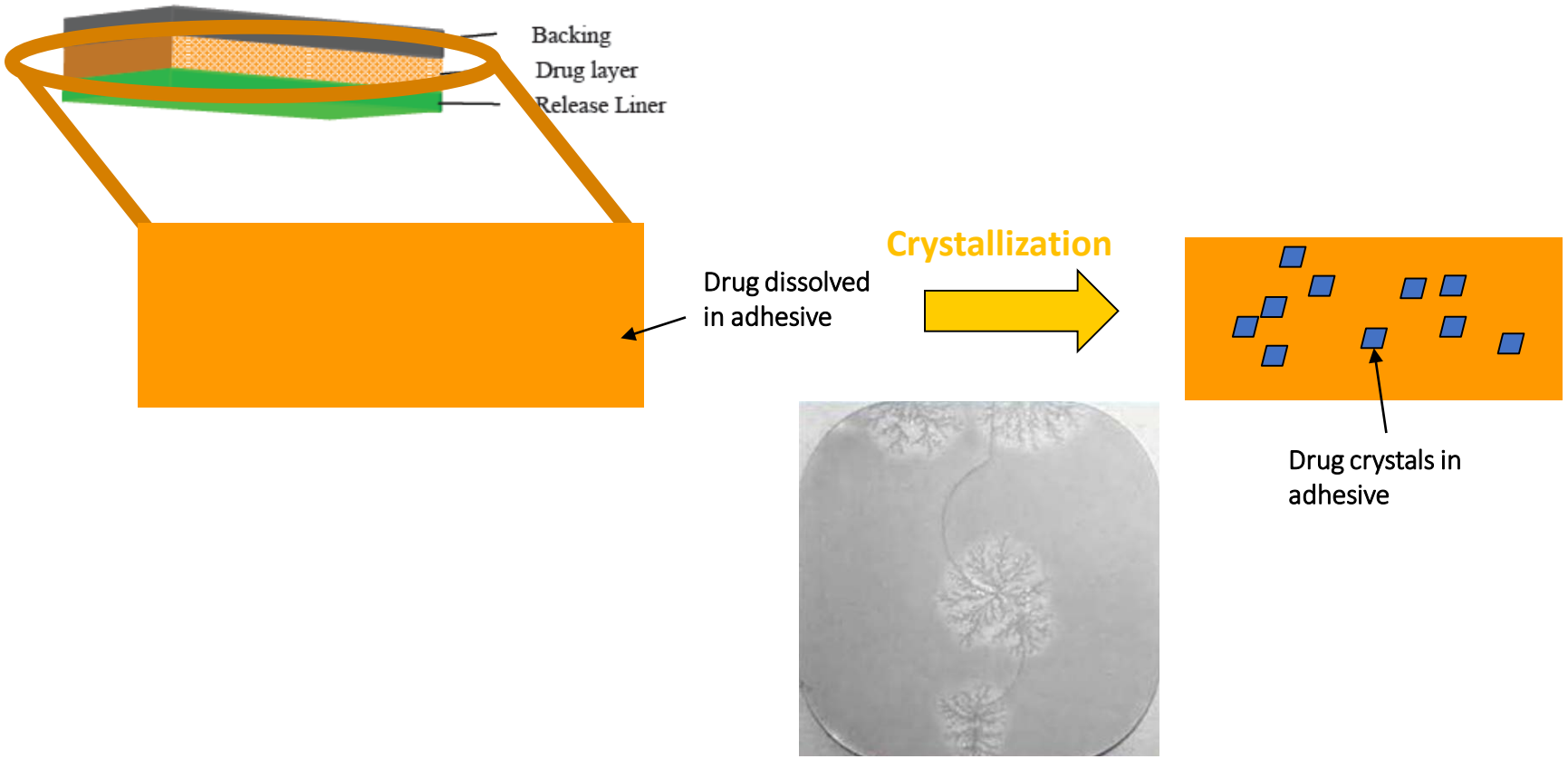
The amount of residual drug substance:

- Has a significant potential to impact quality, efficacy, and safety (including abuse potential)
- Should not exceed that of similar FDA-approved products
- Should be "minimized consistent with the current state of technology"



FDA Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems, August 2011

TDS Design Considerations: Crystallization



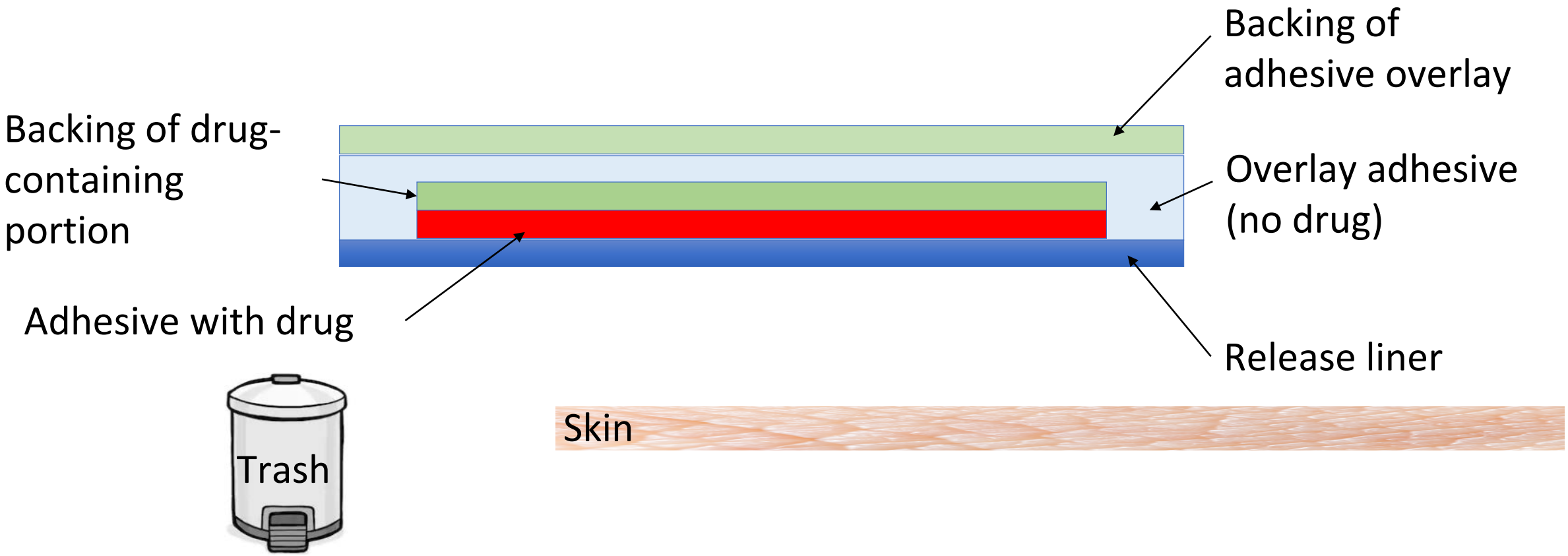
Quality Control of Raw Materials

UNDERSTAND YOUR RAW MATERIALS	
Clinical Concern	Quality Aspects
• Performance: – Adhesion – Drug delivery (Effectiveness) • Safety: – Toxicity – Irritation and sensitization	• Adhesives – "Pharmaceutical grade" typically not offered – Concerns: • Rheological properties • Impurity profile • Lot-to-lot variability • Pouch stock, membranes/films, ink – Concerns: • Extractables/Leachables

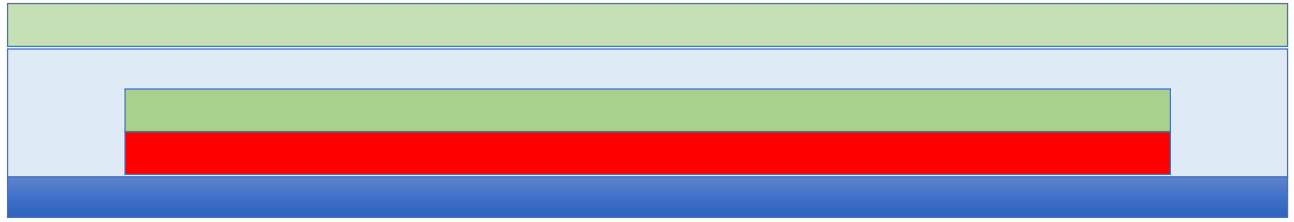
TDS Design Considerations: Overlay

- TDS can be designed to include an adhesive overlay to improve adhesion
- Adhesive overlay: A larger, non-drug-containing patch applied over the active-containing TDS
  - Co-packaged (i.e., adhesive overlay and active TDS are packaged in separate pouches within the same carton)
  - Integrated (i.e., already laminated and packaged as a single unit in a single pouch)
- Buprenorphine TDS is an example of a product with an integrated adhesive overlay

Intended Patient Administration



Efficacy and Safety Concerns



Overlay adhesive
(no drug)

Potential
unintentional
exposure!

Skin

No drug delivery to patient!

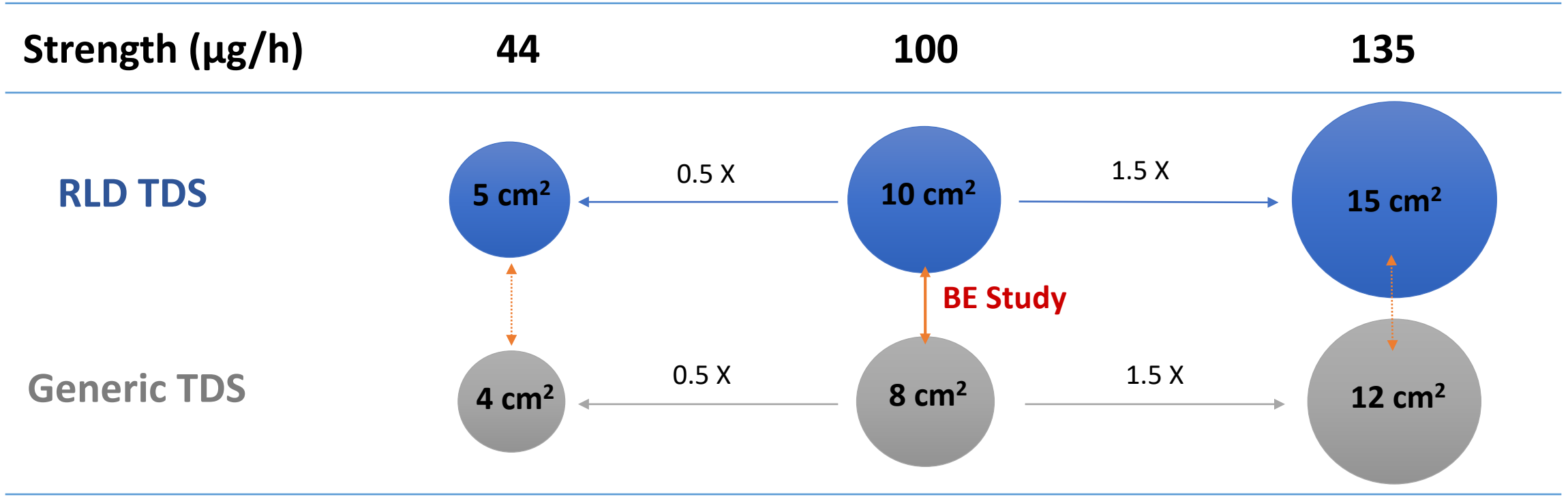
Efficacy and Safety Concerns

- If active part of the TDS remains on the skin
  - Drug would continue to be delivered
- Patient may administer an additional TDS, leading to potential super-therapeutic dose

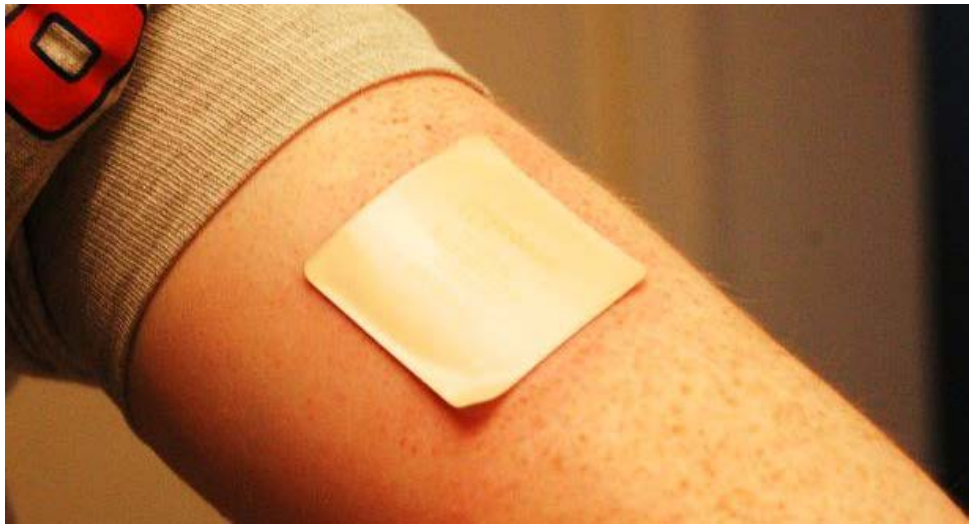
Evaluation of BE and Quality for TDS

- In Vivo Studies With Which to Demonstrate BE for TDS
  - A comparative BE study with pharmacokinetic endpoints
  - A comparative study of the adhesion performance of the TDS
  - A comparative study of the irritation/sensitization potential of the TDS
- An In Vitro Study to Compare the Effects of Heat on TDS
  - A study evaluating the quality of prospective generic TDS, comparing how heat alters the rate and extent of transdermal drug delivery

Considerations for Establishing BE



Considerations for Size/Shape of TDS



Corners may be more prone to lifting, and a long rectangular TDS may experience different torsional strains depending upon the anatomical site and the orientation in which it is applied.

A generic TDS may have a different formulation, size and/or shape; these differences may affect the TDS adhesion to skin.

Study	Test	Reference	Non-Inferior Adhesion
A			May Fail
B			May Pass

Impact of Heat on TDS Performance

Considerations for various scenarios of heat exposure:

- Early heat
- Late heat
- Continuous heat

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

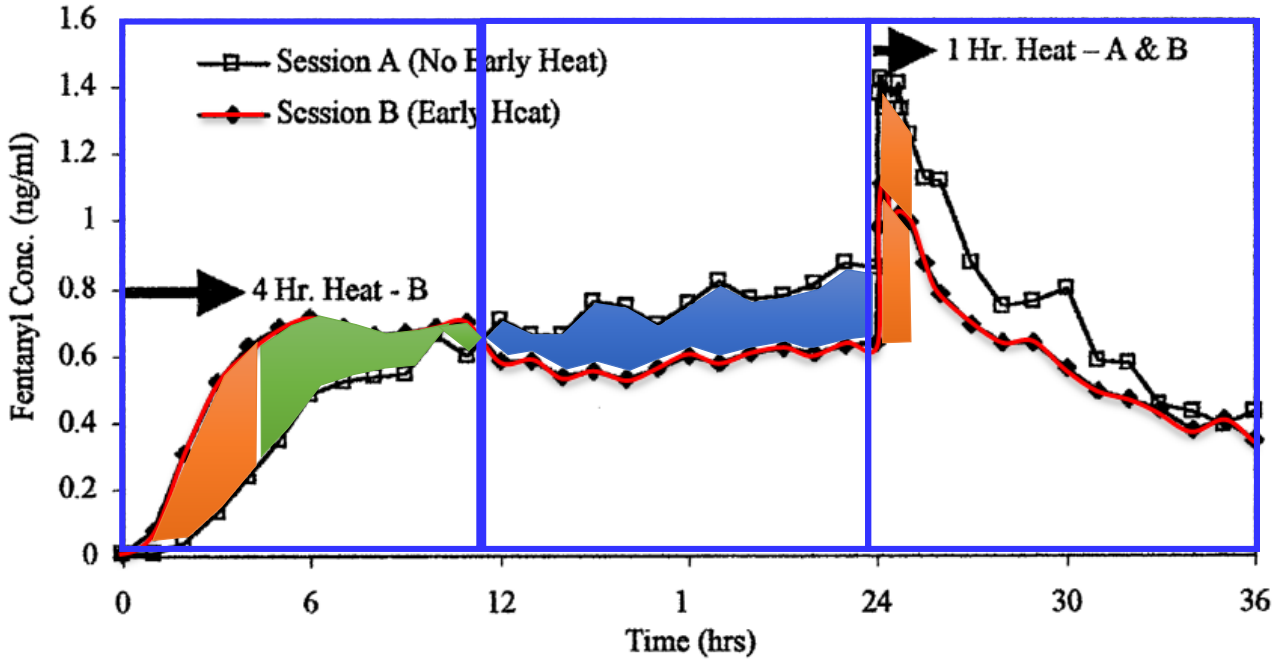
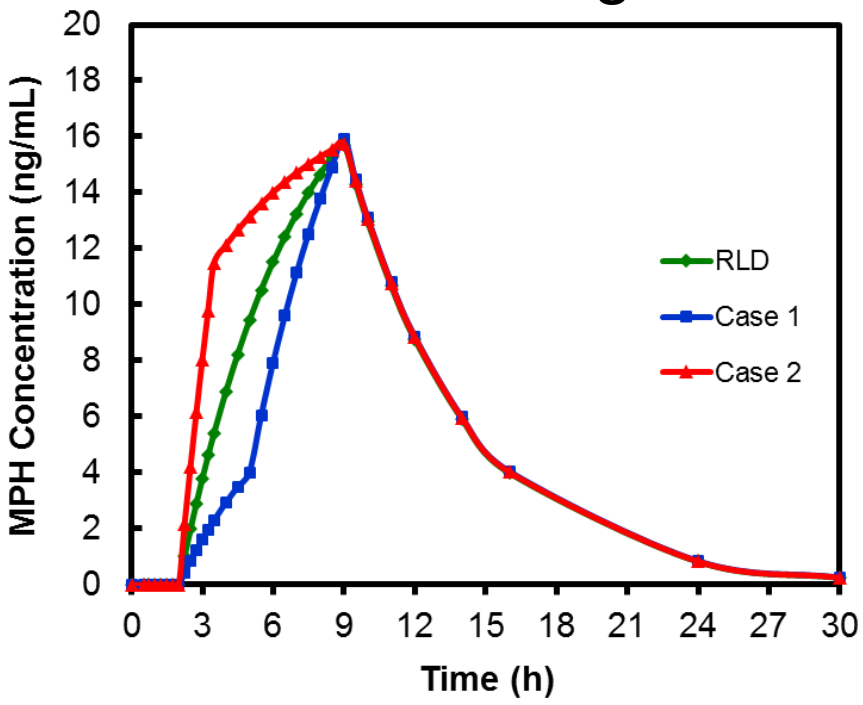


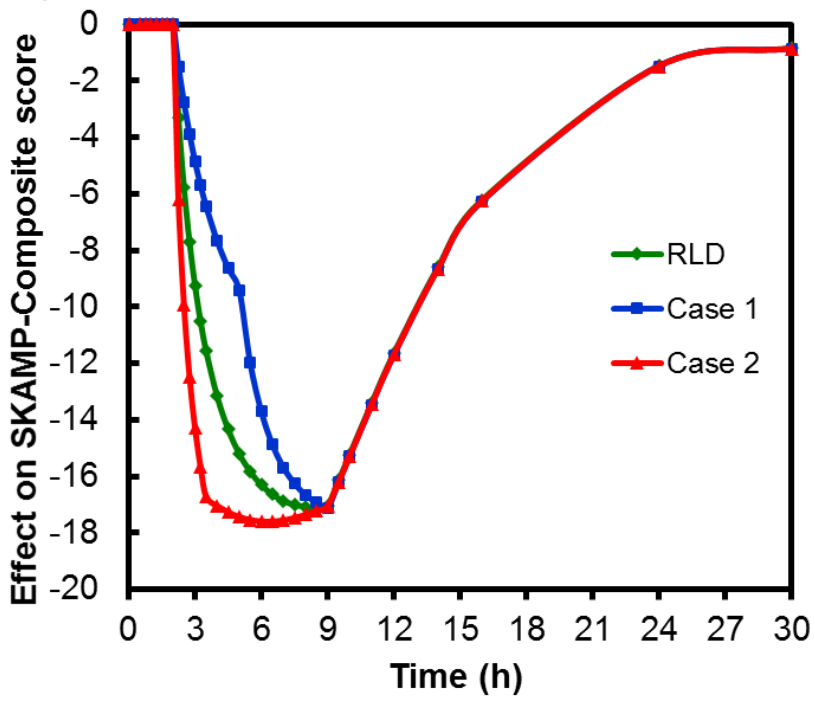
Figure 1. Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

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

Data Analysis Considerations: PK of TDS

- Simulated PK-PD relationship of methylphenidate
  - PK/PD of the Reference Listed Drug (RLD) TDS and 2 hypothetical TDS
  - PD = Swanson, Kotkin, Agler, M-Flynn, Pelham [SKAMP]-Composite score





Data Analysis Considerations: PK of TDS

- Simulated PK-PD relationship of methylphenidate
  - Identified appropriate PK endpoints to ensure that BE ratio limits of 80-125 would be sensitive to potential differences in PD (safety/efficacy)

PK Parameter		Mean estimate			Ratio (Test/RLD)	
		RLD	Case 1	Case 2	Case 1	Case 2
C_{max}	(ng/mL)	15.7	15.9	15.7	1.01	1.00
AUC_t	(ng*h/mL)	150.7	133.5	169.8	0.89	1.13
$pAUC_{2\text{-}9h}$	(ng*h/mL)	67.6	49.5	86.1	0.73	1.27
$pAUC_{2\text{-}12h}$	(ng*h/mL)	103.5	85.8	122.2	0.83	1.18
$pAUC_{5\text{-}9h}$	(ng*h/mL)	52.1	42.9	58.5	0.82	1.12
$pAUC_{9\text{-}12h}$	(ng*h/mL)	35.9	36.3	36.1	1.01	1.01

Data Analysis Considerations: PK of TDS

	Average BE (ABE)	Reference-Scaled ABE (RSABE) Highly Variable (HV) Drug
Criterion	$(\mu_T - \mu_R)^2 \geq \theta^2$	$\frac{(\mu_T - \mu_R)^2}{\max(\sigma_{WR}^2, \sigma_{W0}^2)} \sim \theta_{HV}$
Study Design	Two-sequence, two period crossover design	Two-sequence, four period replicate design; Three-sequence, three period partial replicate design;

μ_T : population average response of the log-transformed measure for the T formulation
μ_R : population average response of the log-transformed measure for the R formulation
σ_{WR}^2 : within-subject variance of the R formulation
σ_{W0}^2 : specified constant within-subject variance
θ_{HV}: predefined BE limit for NTI drug

References

- Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA
- Draft Guidance for Industry: Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs
- Draft Guidance for Industry: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs
- Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems
- Draft Guidance for Industry: Progesterone Oral Capsules
- Strasinger, Caroline et al. (2016). Navigating sticky areas in transdermal product development. Journal of controlled release : official journal of the Controlled Release Society. 233. 10.1016/j.jconrel.2016.04.032

Acknowledgments