Complex Drug-Device Generic Combination Products

October 9-10
Sheraton Silver Spring, MD

Scientific Challenges for Generic Transdermal Products: Recent Advances and Future Research

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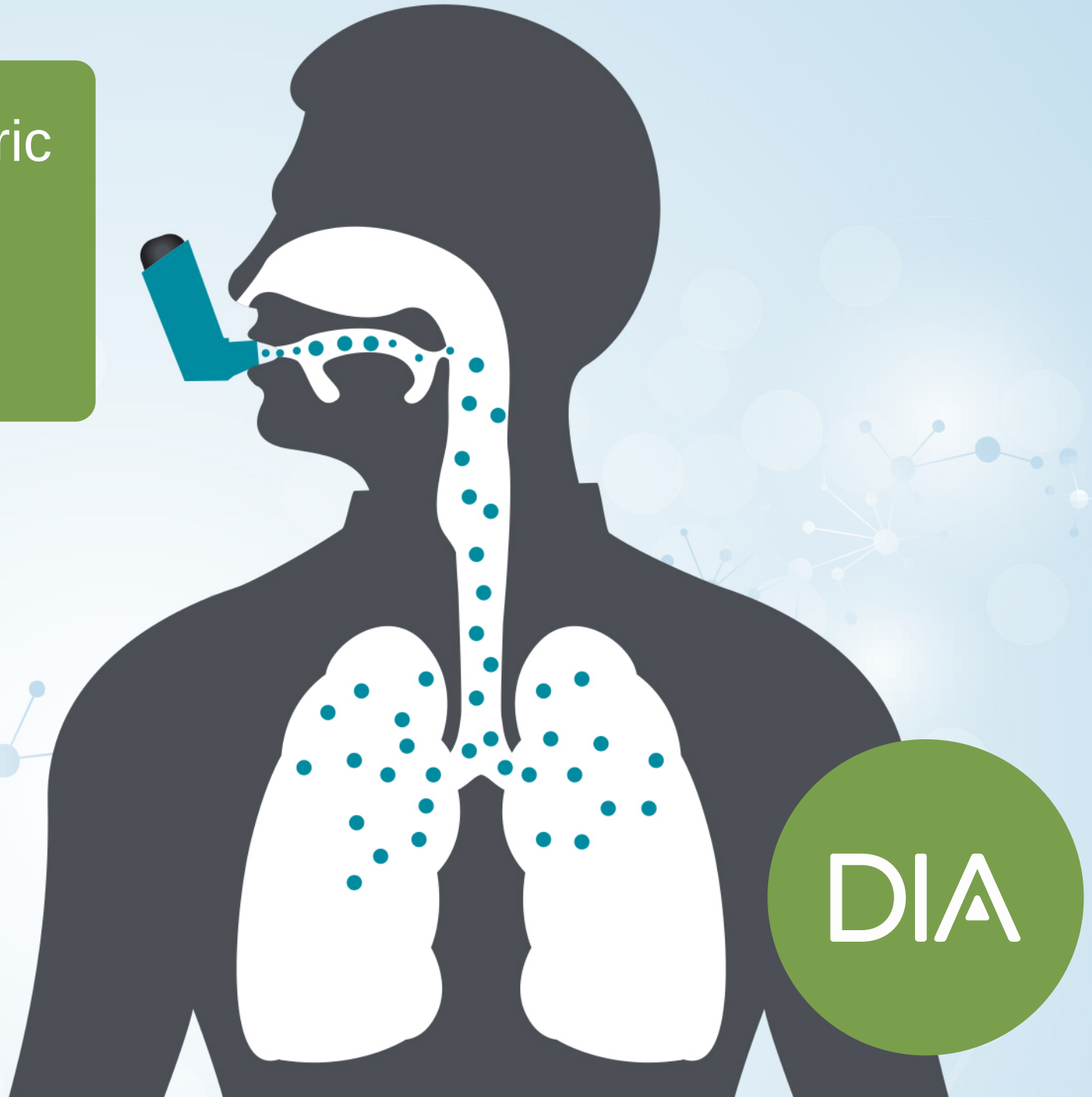

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Factors Affecting Percutaneous Absorption

Drug

- M.W. < 500 Dalton
- Suitable log $P_{oil/water}$
  - High log P (very lipophilic) -> too much retention in the skin
  - Low log P (very hydrophilic) -> difficult to cross the SC
- Unionized molecules cross SC at faster rate

Vehicle/Formulation (Inactive Ingredients)

- Partition coefficient, $k_{membrane/vehicle}$
- pH
- Chemical Penetration Enhancers (CPEs)
- Adhesion/Removal
- Backing layer (occlusivity)
- Shape

Skin

- Hydration level
- Age
- Gender
- Tattoos
- Disease state
- Anatomical location/Follicles
- Irritation

Environmental Factors

- Humidity
- Occlusion
- Heat (high temperature)

Flynn G.L. (2002). Cutaneous and Transdermal Delivery – Processes and Systems of Delivery. In *Modern Pharmaceutics* (pp. 187-235).
Barry B.W. (2007). Transdermal Drug Delivery. In *Aulton's Pharmaceutics: The Design and Manufacture of Medicines* (pp. 565-597).

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Factors Contributing to Adhesion Failure → Product Failure

Device Causes

Backing

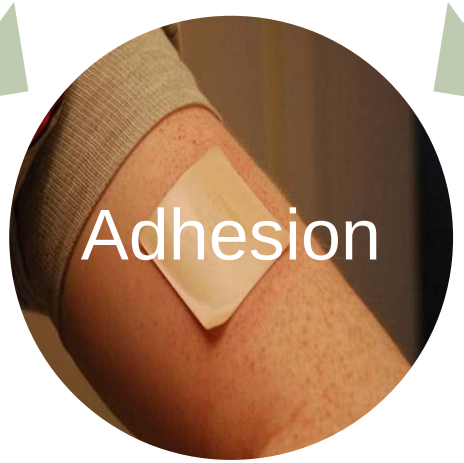
Humidity

Environment Causes

Shape

Occlusivity

Adhesive Formulation or Overlay



Heat

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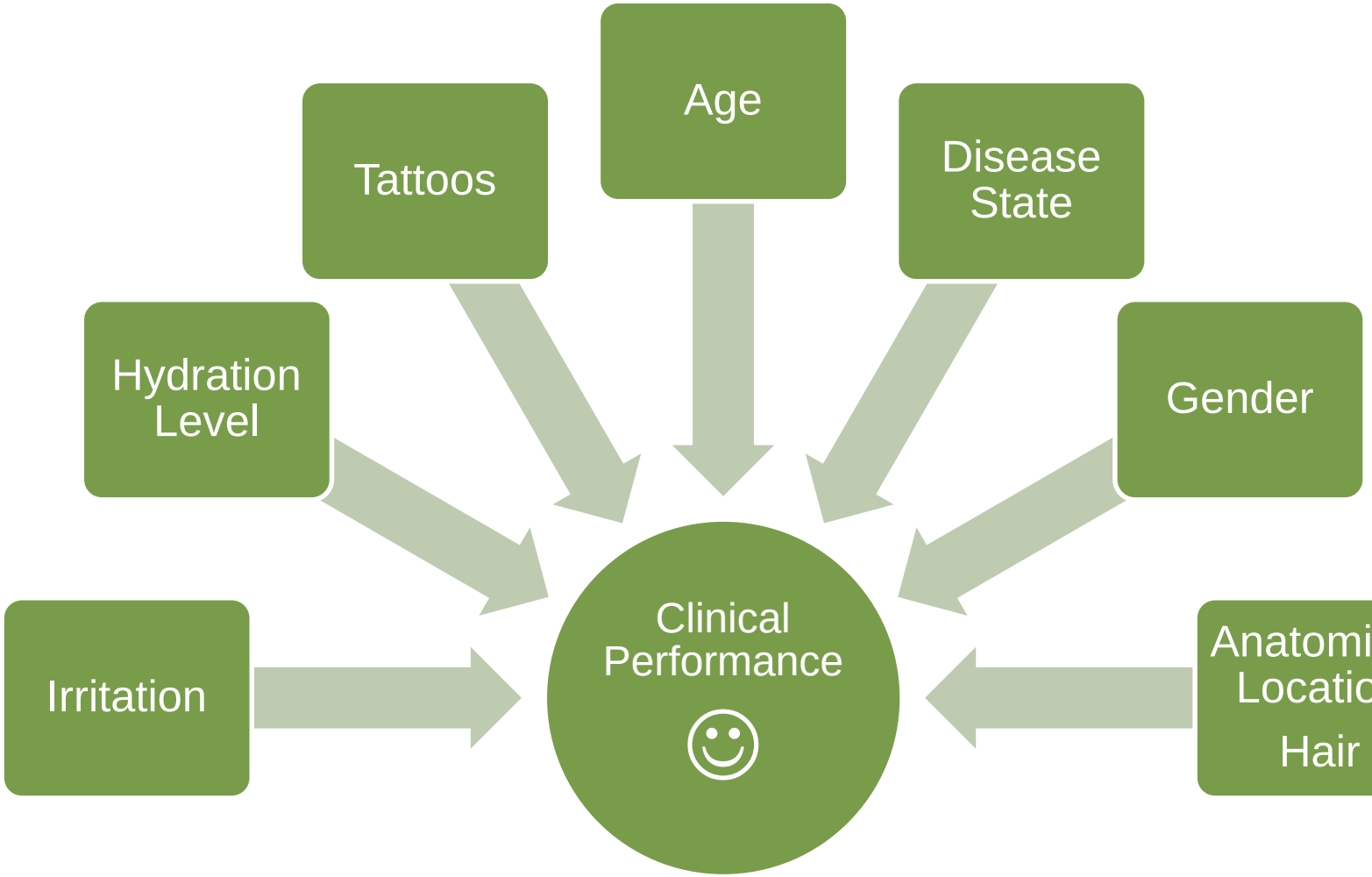
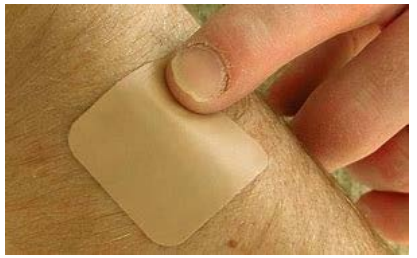
Human Skin Factors Contributing to ➡ Product Failure





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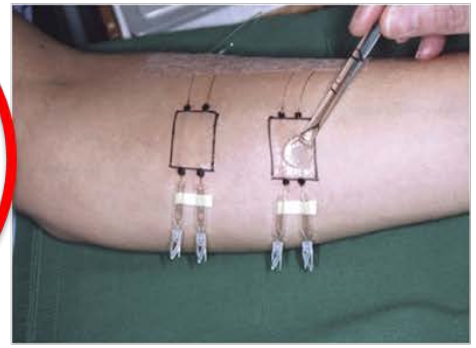
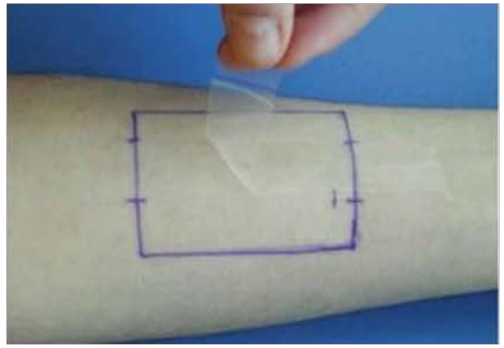
Our Research Focus: Methods of Assessment of Bioavailability

IVPT

Microdialysis



Tape stripping



Blood levels

Pharmacodynamic assay (vasoconstriction)

Urine levels

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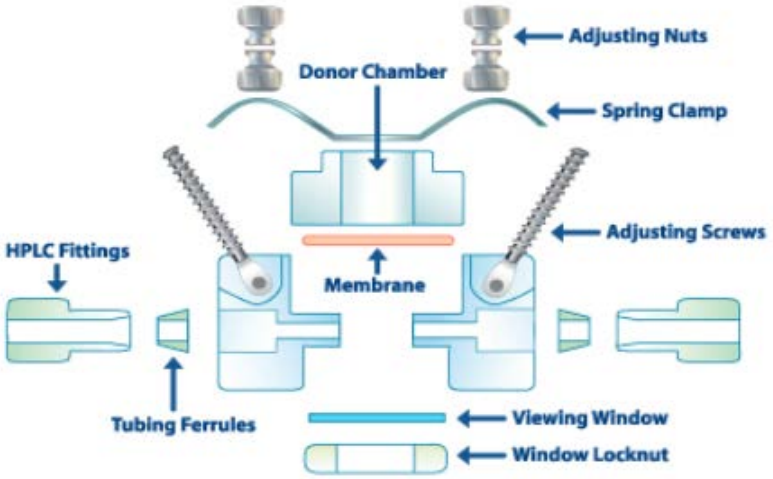
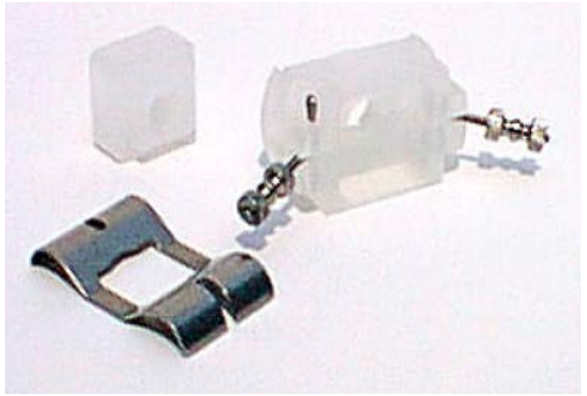
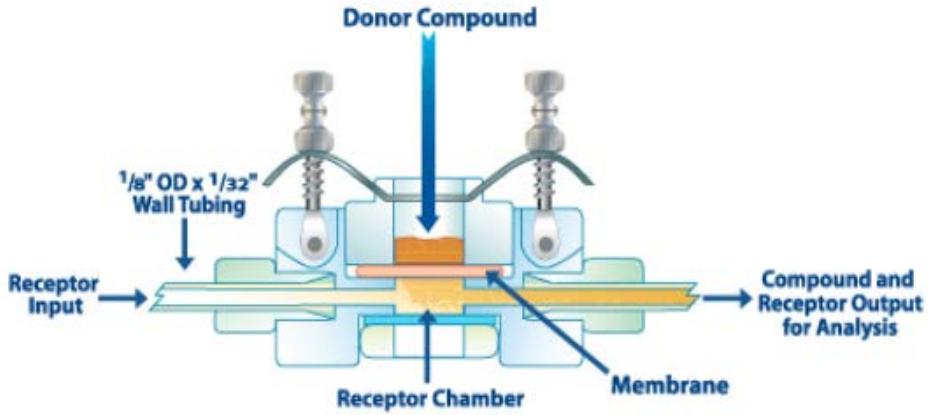
In-Line Diffusion Cells







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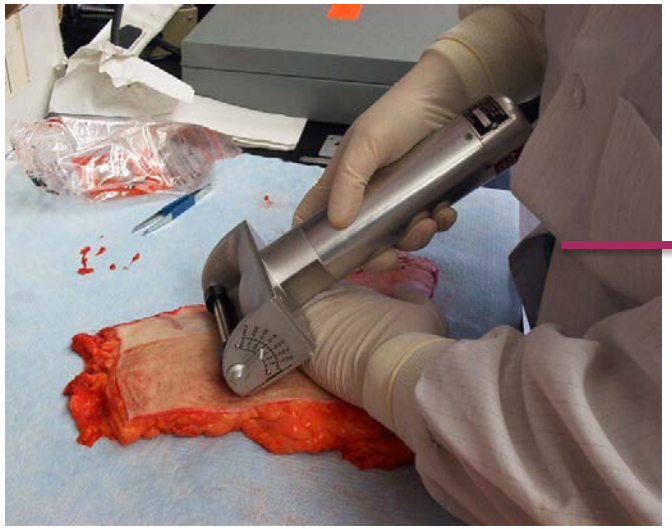
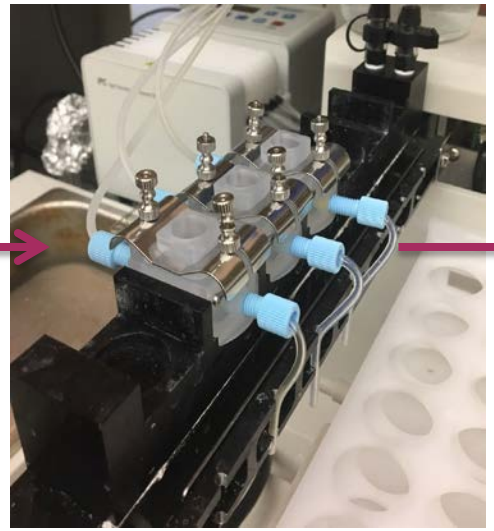
http://permegear.com/in-line-cells/

IVPT: *In vitro* permeation test

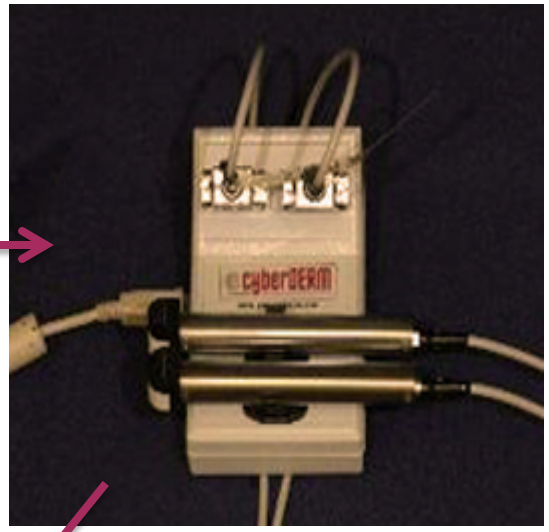
1. Dermatome



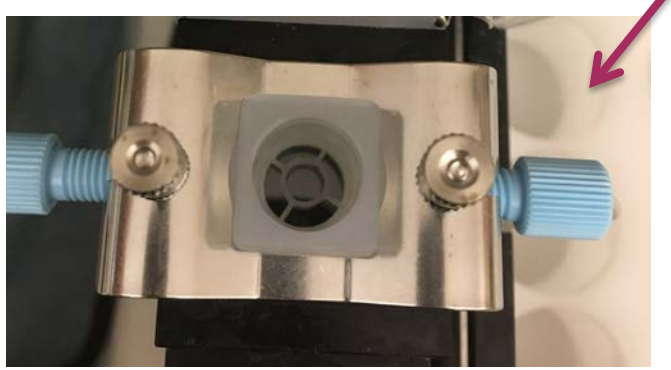
2. Assemble setup



3. Record TEWL



4. Dose Product



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IVIVC: *In Vitro In Vivo* Correlation

- Value of IVIVC
  - Facilitate testing of drug candidates and optimization of formulation
  - Assist in quality control
  - Serve as a surrogate for bioequivalence studies, scale-up and postapproval changes

→ Minimize/Reduce in vivo clinical studies (Save  & )

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IVIVC: *In Vitro In Vivo* Correlation

- Definition[1]: "a predictive mathematical model describing the relationship between an *in-vitro* property of a dosage form and an *in-vivo* response"
- Level A: a point-to-point correlation between *in vitro* and *in vivo* profiles
- Level B: comparison between *in vitro* dissolution time and *in vivo* residence time
- Level C: a single point correlation between *in vitro* and *in vivo* parameters

Level A is most informative and useful

[1] FDA Guidance for Industry: extended release oral dosage forms: development, evaluation and application of in vitro/in vivo correlations

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TDS Strength/Dose Study
IVIVC without Heat Effect: Fentanyl TDS, 25 µg/h

	Duragesic®	Mylan
Drug Load (mg)	4.20	2.55
Size (cm^2)	10.50	6.25
Thickness (µm)	110	190
Adhesive	Polyacrylate	Silicone
Other Inactive Ingredients	Polyester/ ethyl vinyl acetate backing film, copovidone	Dimethicone NF, polyolefin film backing
Appearance		

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Study Designs

In Vitro (IVPT)	In Vivo (Human PK Studies)

• Two-way crossover study
  • Duragesic® fentanyl TDS
  • Mylan fentanyl TDS
 	
• 3 donors with 3-4 replicates per donor
 	
• TDS applied for 72 h; IVPT sampling up to 72 h
	• Three-way crossover study
	  • Intravenous (IV) fentanyl citrate
	  • Duragesic® fentanyl TDS
	  • Mylan fentanyl TDS
	
	• 16 healthy adults completed
	
	• TDS applied for 72 h; PK sampling up to 192 h (8 days)

PK parameters from each study subject were used for IVIVC evaluations

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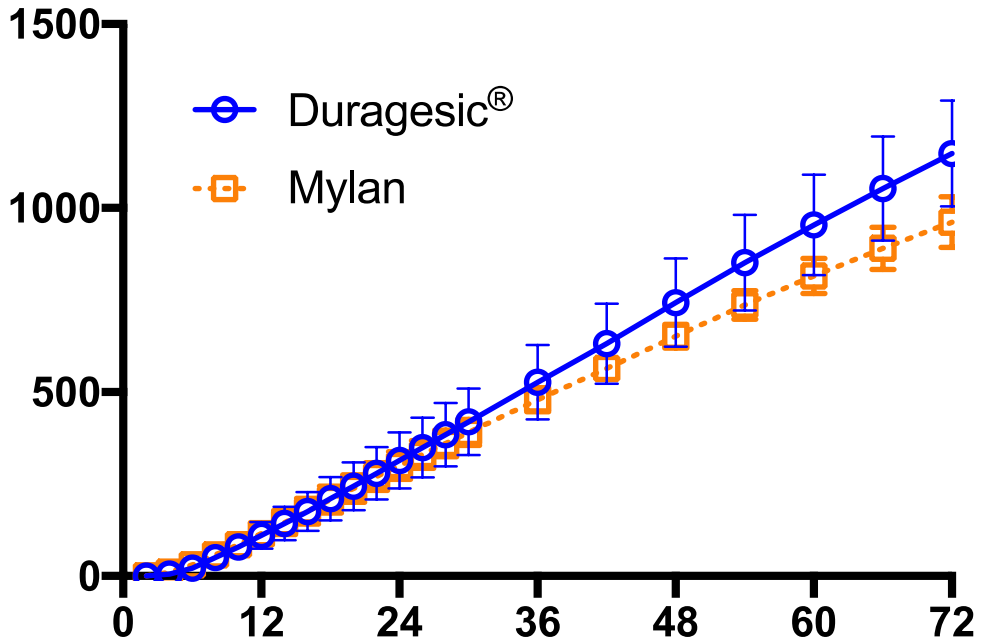
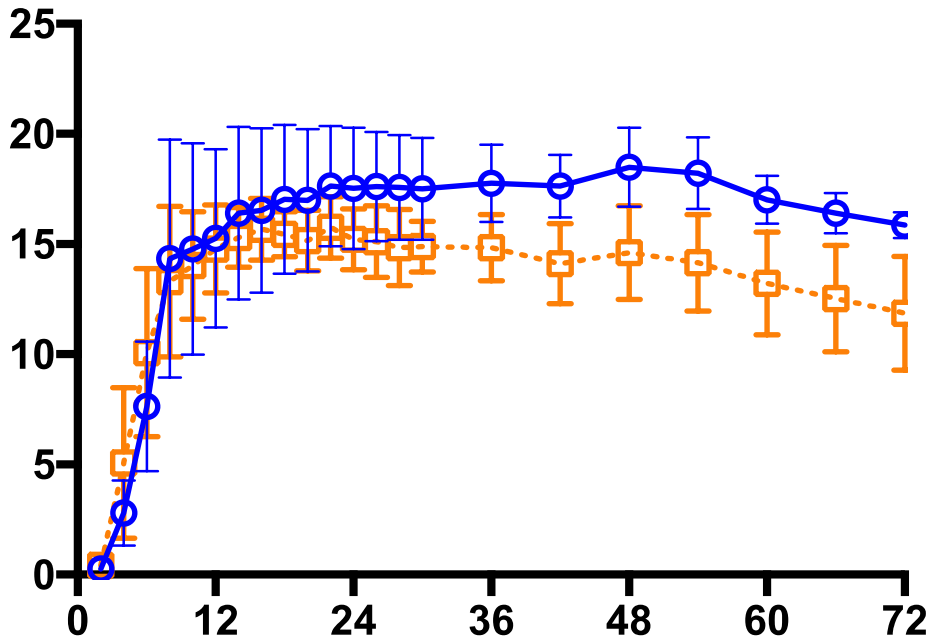
IVPT Results

Mean ± SEM from 3 donors
with n=3-4 per donor





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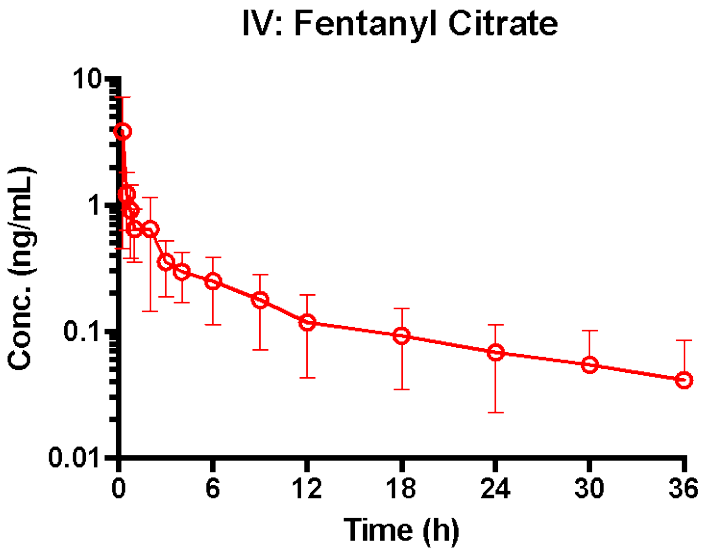
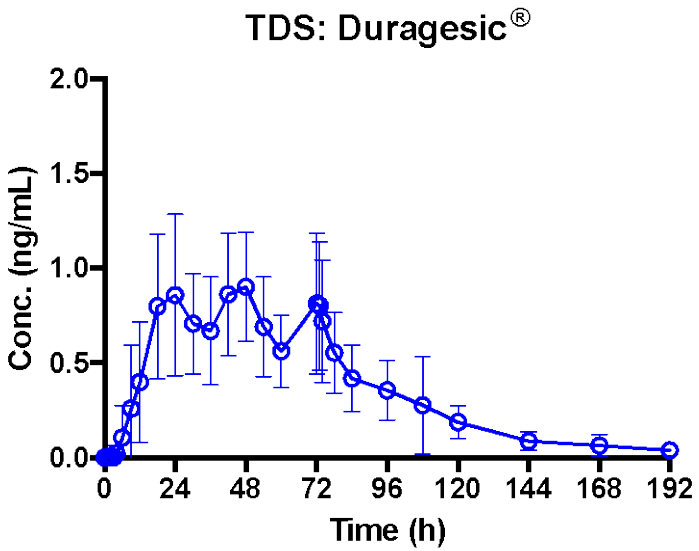
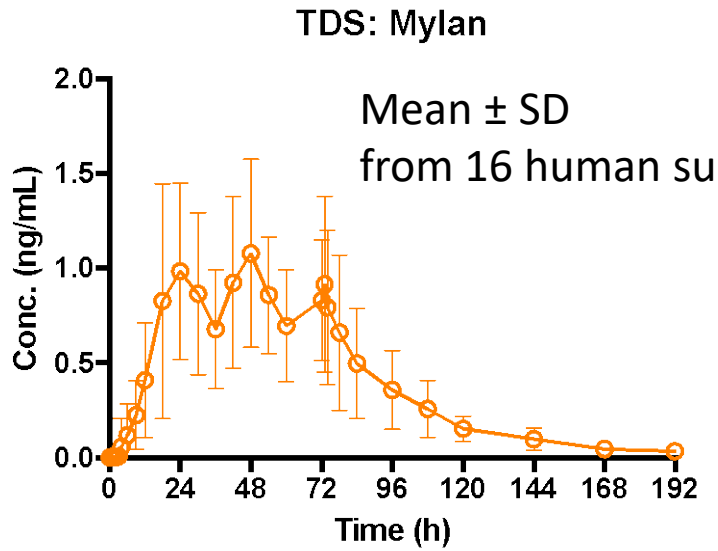
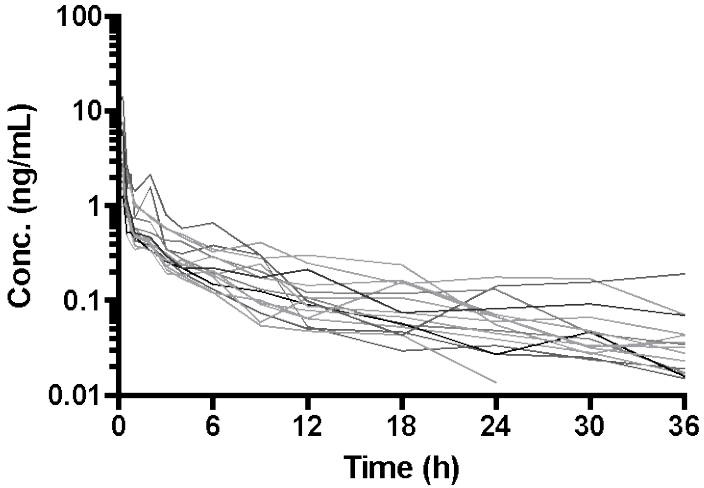
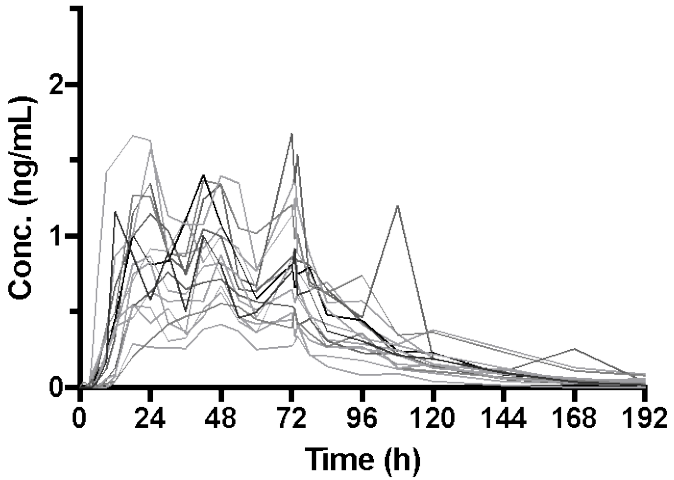
In Vivo Results

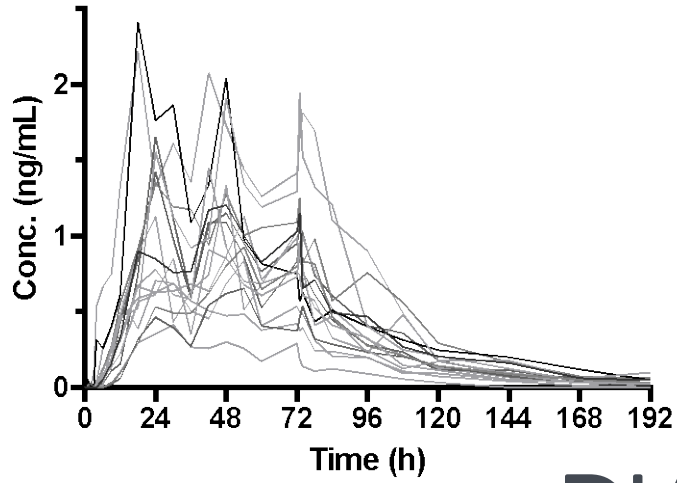












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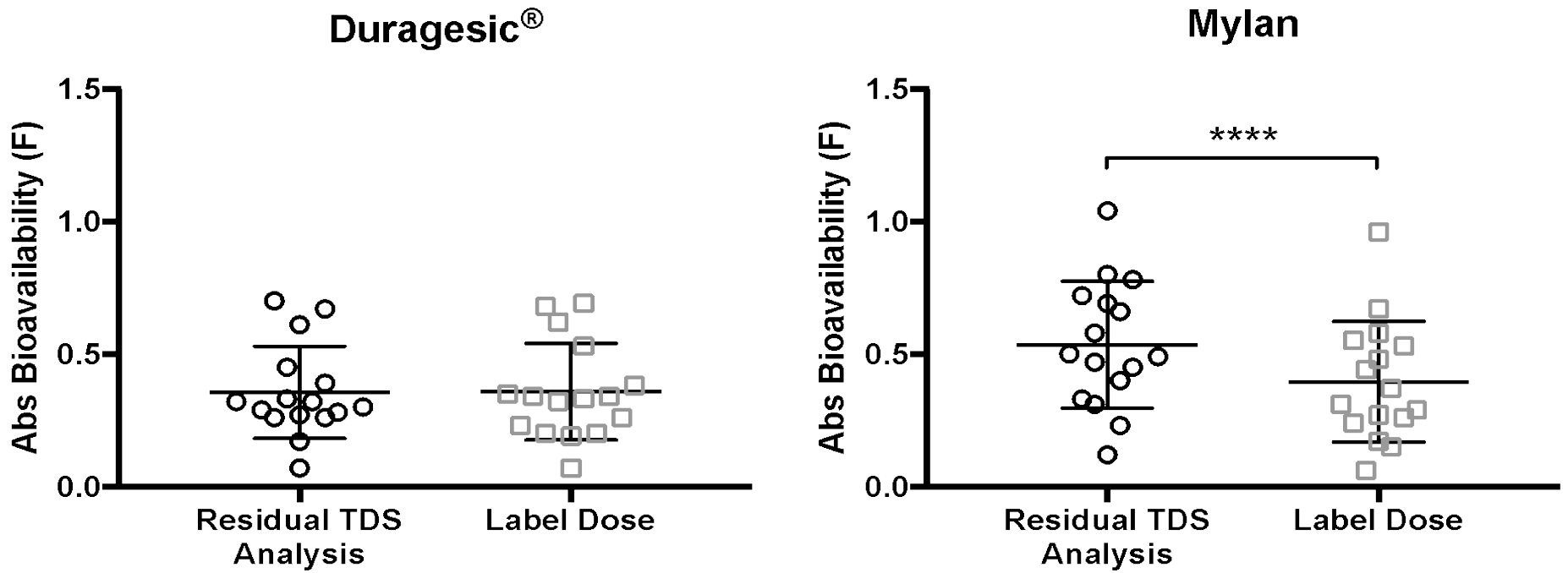
Absolute Bioavailability (F)

$$\frac{AUC_{0-\infty,TDS} \times Dose_{IV}}{AUC_{0-\infty,IV} \times Dose_{TDS}}$$

1) Dose determined from residual TDS analysis ($X_{DELIVERED}$)

$$X_{DELIVERED} = X_{Control\ (unused)} - X_{Remaining\ after\ 72\ h\ of\ wear}$$

2) Label Dose (25 µg/h × 72 h = 1800 µg)



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Level C IVIVC: Steady-state Concentration (C_{ss})

$$C_{ss} = \frac{J_{ss} \times F \times A}{CL}$$

C_{ss}: Predicted steady-state concentration
J_{ss}: Steady-state flux obtained from IVPT
F: Absolute bioavailability for TDS
A: area (size) of TDS
CL: Total body clearance obtained from study subjects

	Observed C_{ss} in vivo (ng/mL)	Predicted C_{ss} from IVPT (ng/mL)	p-value (significance)
Duragesic®	0.76 ± 0.27	0.65 ± 0.07	>0.5146 (ns)
Mylan	0.87 ± 0.34	0.80 ± 0.10	>0.7550 (ns)

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Level A IVIVC: Method I example

	Prediction while TDS was worn	Prediction after TDS removal
Method I	$C_s = \frac{F \cdot R_{in}}{CL} \cdot \left(1 - e^{-kt}\right)$	$C_s = C_0 \cdot e^{-\left(\frac{\ln 2}{t_{1/2,TDS}}\right)t}$

C_s: Predicted in vivo serum concentration
F: Absolute bioavailability for TDS
R_{in}: Rate of input (mean flux during steady-state in IVPT experiments)
CL: Total body clearance
k: Elimination rate constant
t: Time after administration of TDS
C_0: Predicted initial concentration after TDS removal
V_d: Volume of distribution

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Level A IVIVC: Example Method I

$$C_s = \frac{F \cdot R_{in}}{CL} \cdot \left(1 - e^{-kt}\right)$$

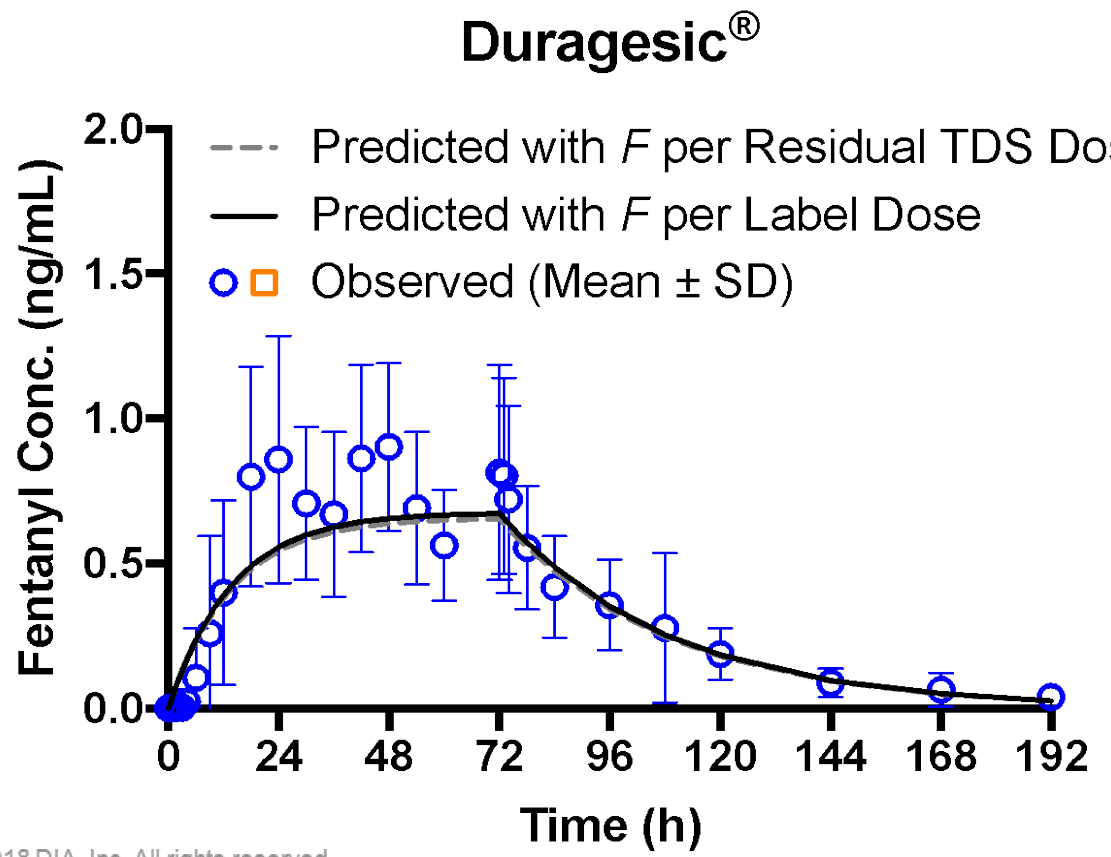
$$C_s = C_0 \cdot e^{-\left(\frac{\ln 2}{t_{1/2,TDS}}\right)t}$$

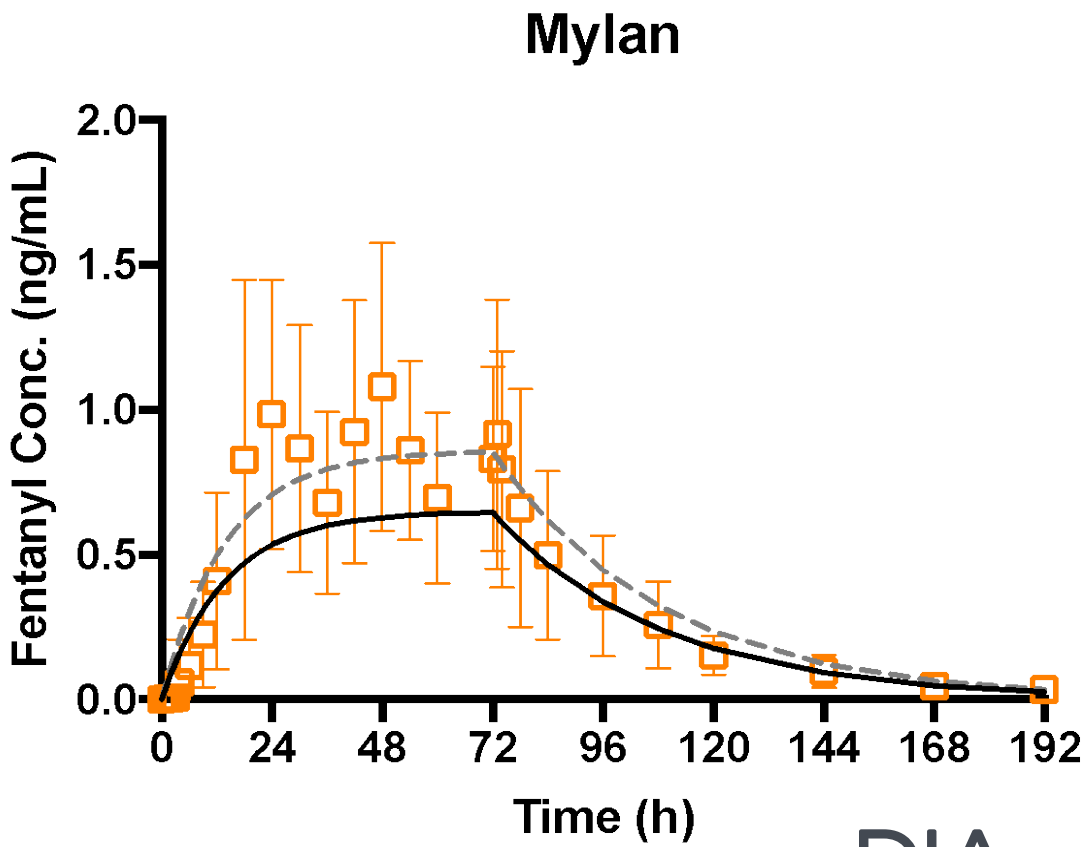
F

1) Dose determined from residual TDS analysis

$$X_{DELIVERED} = X_{Control\ (unused)} - X_{Remaining\ after\ 72\ h\ of\ wear}$$

2) Label Dose (25 µg/h × 72 h = 1800 µg)





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Summary of Recent Work

Bioavailability and IVIVC for Fentanyl TDS Under the Normal Temperature Condition

IVPT using human skin & In vivo PK Studies in human

- Residual TDS analysis was shown to provide useful information in addition to PK data in characterizing the extent of drug delivery and absorption from TDS

- Good IVIVC results for fentanyl TDS
  - IVPT is useful in predicting in vivo performance of TDS
  - Normal temperature conditions
  - PK parameters directly obtained from study subjects

- Further work studying IVIVC between IVPT and in vivo PK data for a diverse set of drug molecules would help to better understand the usefulness and limitations of IVPT

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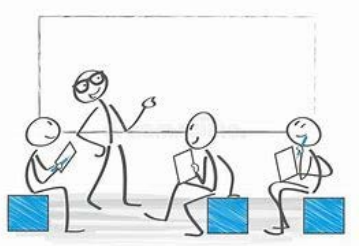
Factors Contributing to Adhesion Failure → Product Failure

Device Causes



Shape

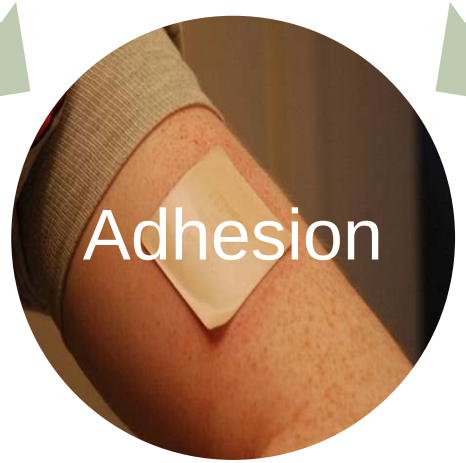
Backing

Humidity

Environment Causes

Occlusivity

Adhesive Formulation or Overlay



Heat

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Human Skin Factors Contributing to ➡ Product Failure

Tattoos

Age

Disease State

Hydration Level

Gender

Irritation

Clinical Performance ☺

Anatomical Location

Hair

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- Sherin Thomas (Lidocaine, buprenorphine, diclofenac)
- Dana Hammell, MS (Lab Manager and Document Control)
- Dani Fox (Clinical Coordinator)
- Sagar Shukla (Lidocaine)
- Paige Zambrana (Sunscreens & glucose monitoring, fentanyl)
- Qingzhao Zhang (Metronidazole & rivastigmine)
- Past: Juliana Quarterman
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  TDS Heat Effects & IVIVC
- Dr. Priyanka Ghosh, OGD
  TDS Heat Effects & IVIVC

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