



# In Vitro and In Vivo Evaluation of Three Fentanyl Transdermal Delivery Systems In Conjunction With Transient Heat Exposure

**Soo Hyeon Shin**, Mingming Yu, Juliana C. Quarterman, Dana C. Hammell, Hazem E. Hassan, Audra L. Stinchcomb



Dermatopharmaceutics Focus Group Meeting


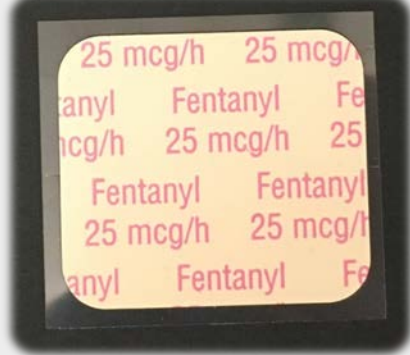



# Why is Heat effect on TDS of Interest?

- Many sources of heat:
    - Heating pads
    - Saunas
    - Hot tubs
    - Sunbathing
    - Prolonged activity under direct sunlight
  - Multiple **life-threatening** incidents when TDS was exposed to **heat**
  - In 2008, FDA required labeling change for Duragesic<sup>®</sup> fentanyl TDS (RLD) to include a warning against heat
- ⇒ Same change required for generic fentanyl TDS



# Study Products: Fentanyl TDSs, 25 $\mu\text{g}/\text{h}$

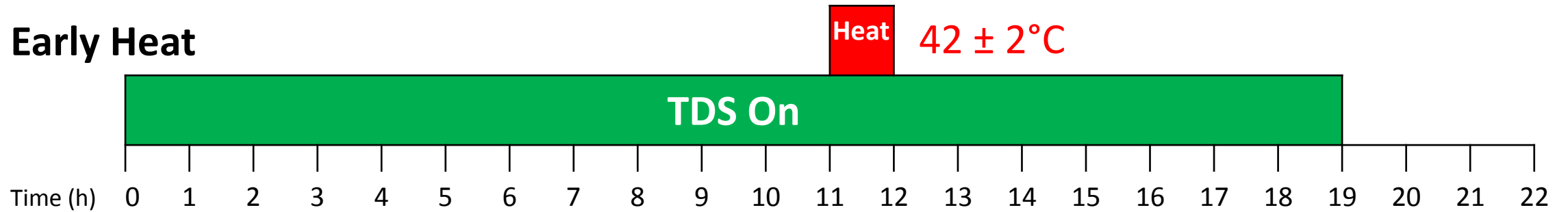
|                             | <b>Duragesic<sup>®</sup></b>  | <b>Apotex</b>  | <b>Mylan</b>   |
|-----------------------------|---|--|--|
| Drug Load (mg)              | 4.20  | 2.76   | 2.55   |
| Size (cm <sup>2</sup> )     | 10.50   | 10.70  | 6.25   |
| Thickness ( $\mu\text{m}$ ) | 110   | 200  | 190  |
| Adhesive                    | Polyacrylate  | Polyisobutene  | Silicone   |
| Other Inactive Ingredients  | Polyester/<br>ethyl vinyl acetate backing<br>film, copovidone                       | Isopropoyl myristate,<br>octyldodecanol,<br>polybutene, polyethylene/<br>aluminum/ polyester film<br>backing | Dimethicone NF,<br>polyolefin film backing   |
| Appearance                  |  |                          |  |



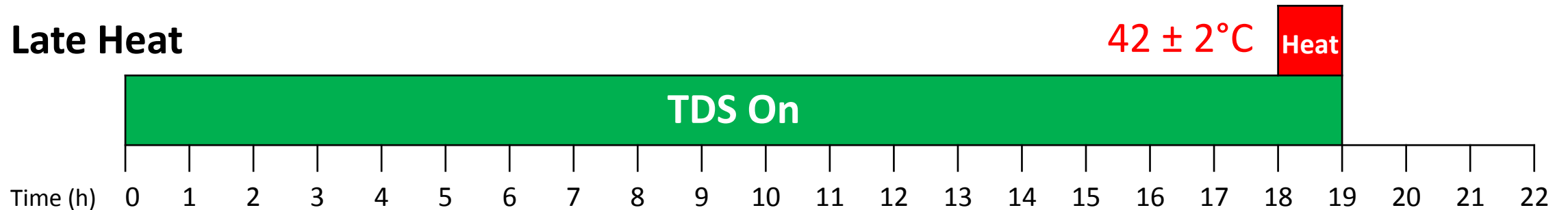
# Study Designs for In Vitro and In Vivo Studies

- A six-way, crossover study with 3 fentanyl TDSs

## Early Heat



## Late Heat

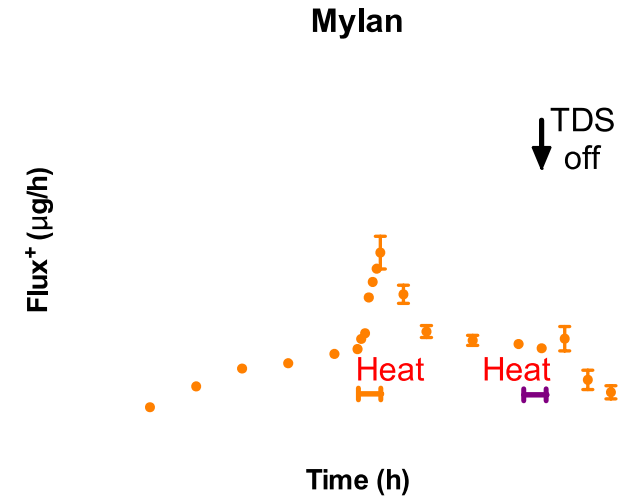
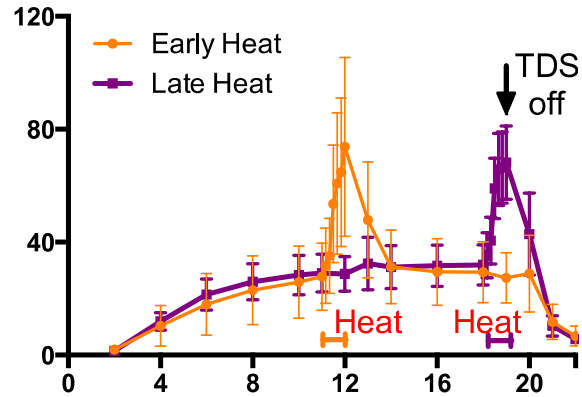




# Results

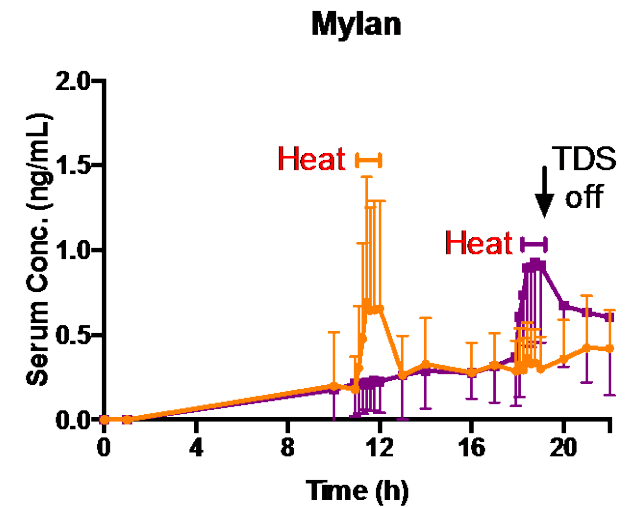
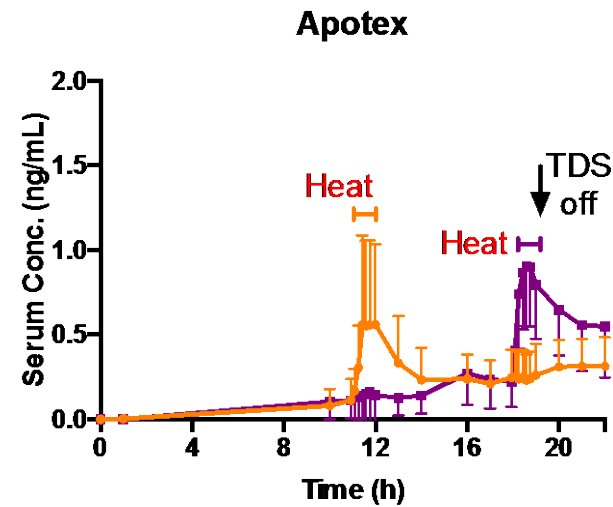
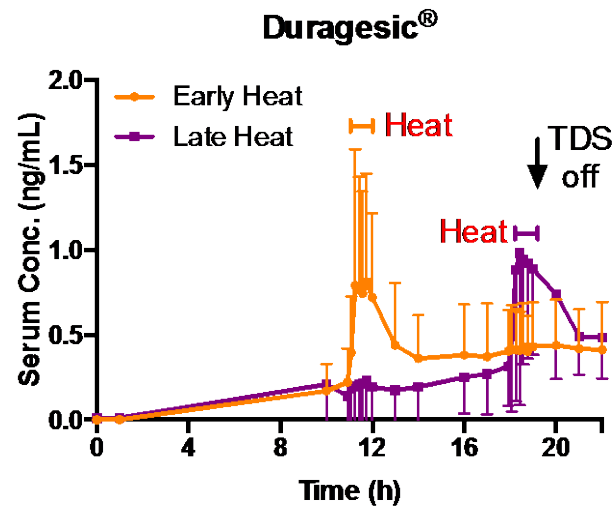
## In Vitro

Flow-through In-Line diffusion system  
Mean  $\pm$  SEM from 3 donors,  
n=4 per donor



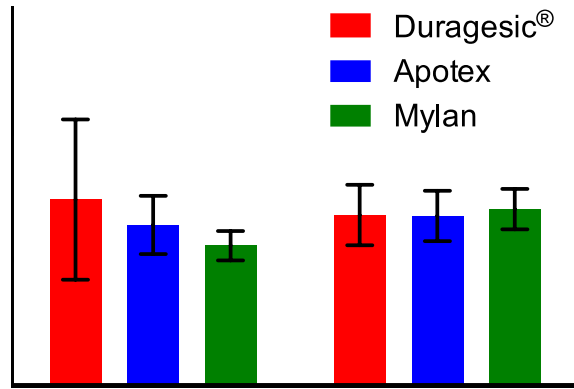
## In Vivo

Mean  $\pm$  SD from  
7 healthy adults



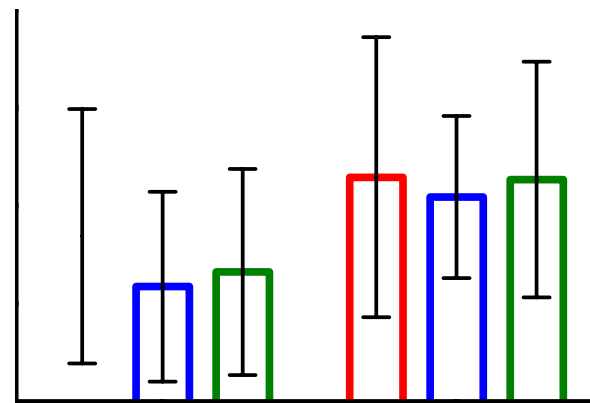


# Results – Heat Effect



No significant difference ( $p > 0.05$ ) was found among three TDSs for all comparisons.

(two-way ANOVA, followed by Bonferroni's post-hoc analysis).



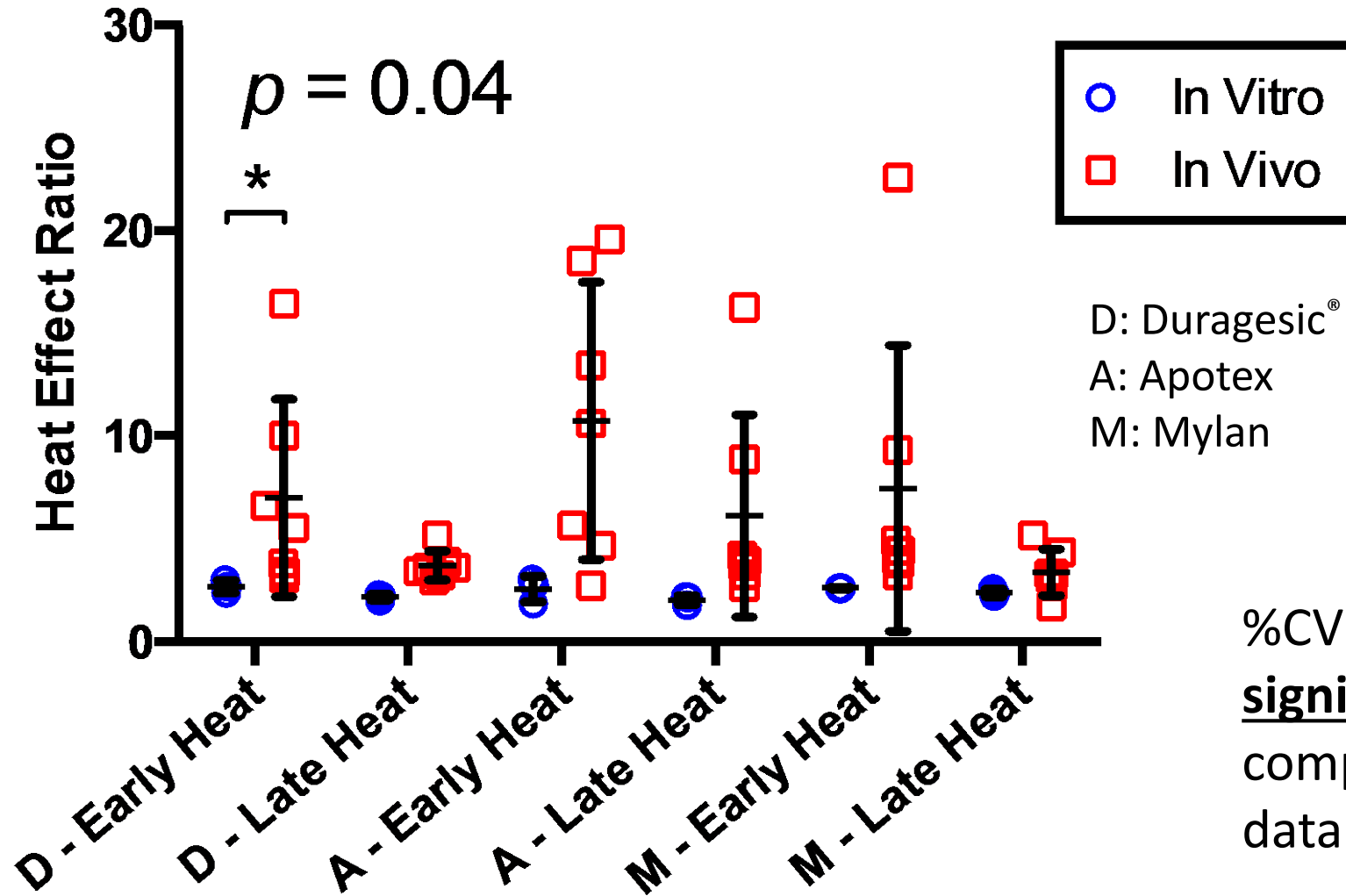
Heat effect window:

- Early Heat: 11 – 14 h
- Late Heat: 18 – 21 h



# Results – Heat Effect Ratio

the ratio of  $J_{max}$  (for in vitro) or  $C_{max}$  (for in vivo) during the 3h heat effect window and the value immediately before the heat exposure.



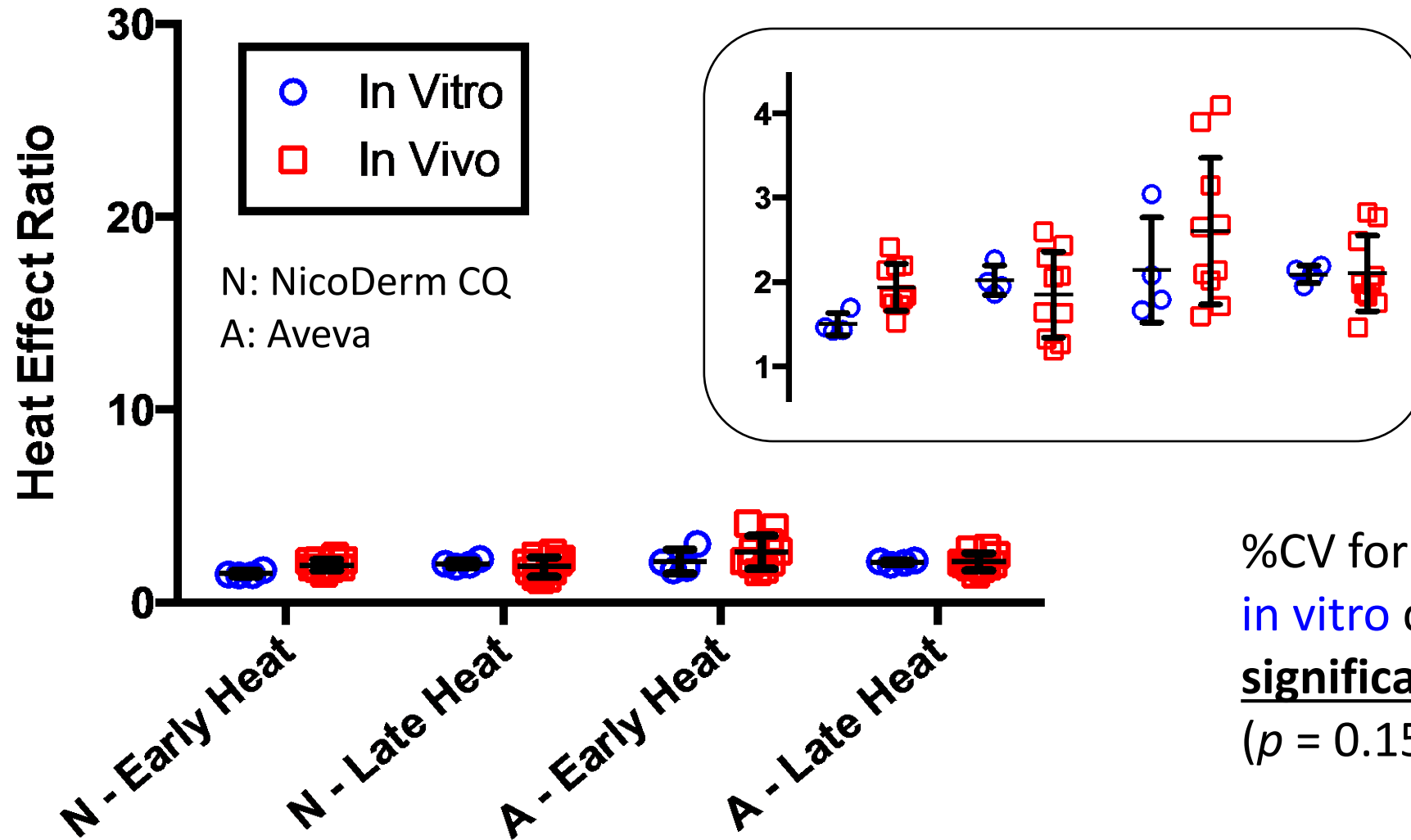
%CV for **in vivo** data was **significantly higher** ( $p = 0.01$ ) compared to %CV for **in vitro** data



# Results – Heat Effect Ratio

the ratio of  $J_{max}$  (for in vitro) or  $C_{max}$  (for in vivo) during the 3h heat effect window and the value immediately before the heat exposure.

## Nicotine TDS



%CV for **in vivo** data and **in vitro** data was not significantly different ( $p = 0.15$ )





# Conclusions

- Comparable heat effect among three fentanyl TDSs
  - From both in vitro and in vivo studies
- The observed heat effect was higher in vivo, compared to in vitro
  - % CV also higher in vivo
- When evaluating heat effects in vitro, the physiological effects in the skin, microcirculation and subcutaneous tissues in human subjects need to be considered
- Appropriate analyses to define and compare heat effects need to be further explored



# Acknowledgments

## Advisors

- Dr. Hazem Hassan
- Dr. Audra Stinchcomb

## Co-Authors

- Dr. Mingming Yu
- Juliana Quarterman
- Dana Hammell

## U.S. FDA

- Dr. Sam Raney
- Dr. Priyanka Ghosh
- Dr. Markham Luke

## Clinical Study Team

- Dr. Samer El-Kamary
- Dr. Wilbur Chen
- Melissa Billington
- GCRC nurses at UMB

## Clinical Study Participants

## Funding



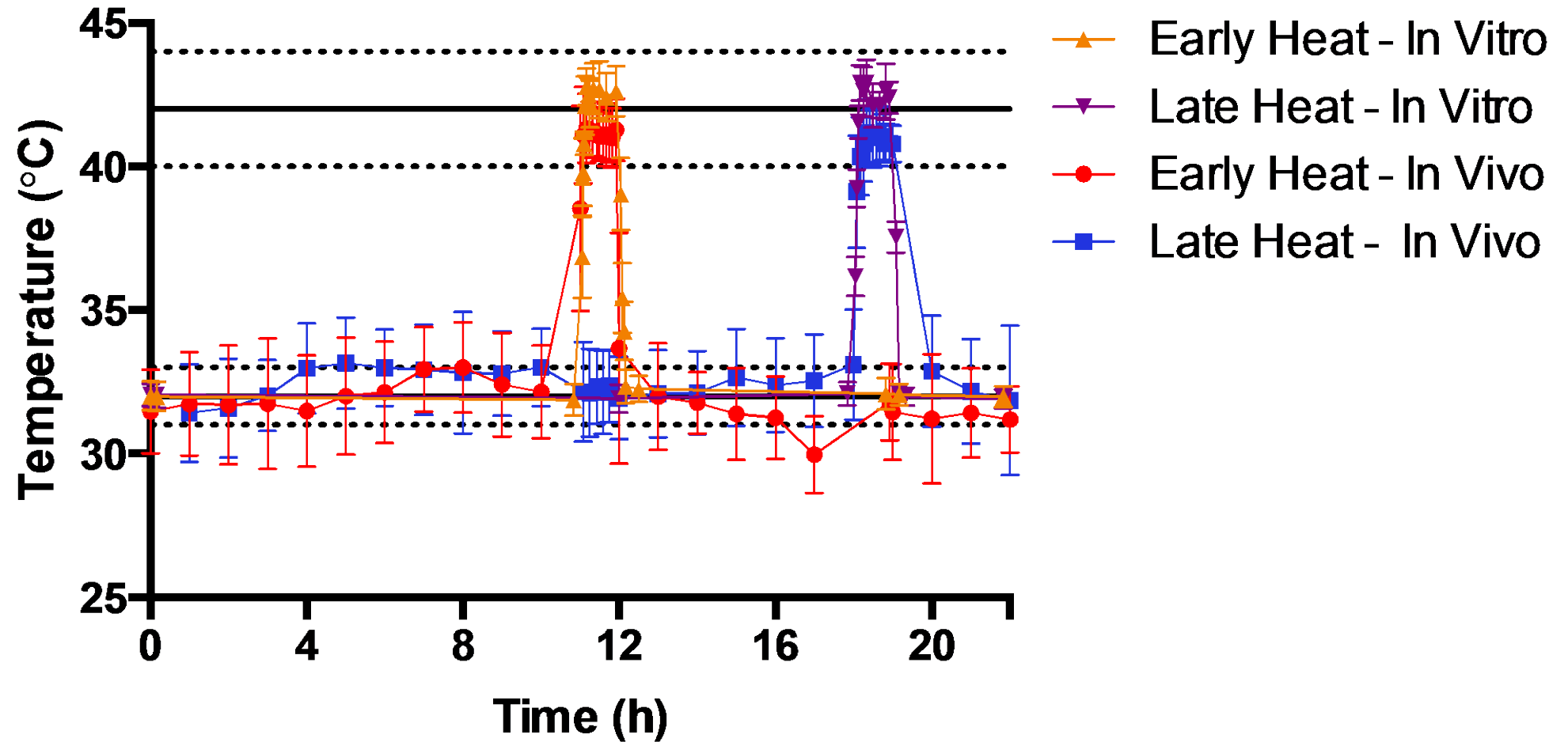
- Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD004955. The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.



# Back-up Slides



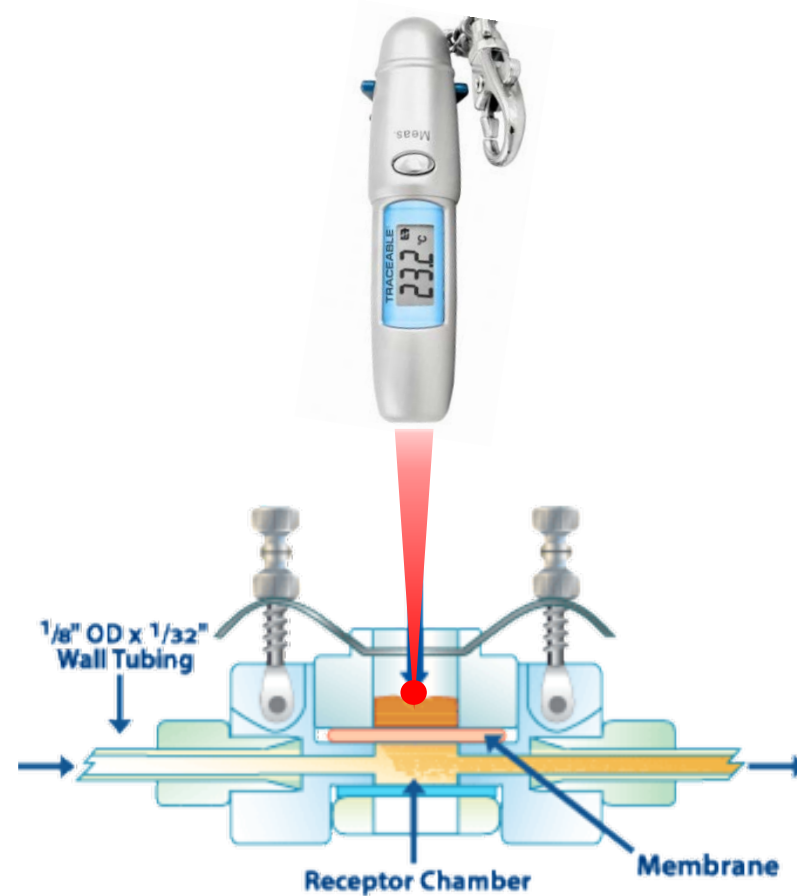
# Temperature Monitoring





# Temperature Monitoring In Vitro

- Infrared Thermometer





# Heat application and Temperature Monitoring In Vivo



- Kevlar sleeve with an opening to expose TDS, while protecting skin from other areas
- Thermometer probe adjacent to TDS

- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad



# Heat Effect In Vivo: Fentanyl vs. Nicotine

