# CHALLENGES AND OPPORTUNITIES OF COMPLEX CLINICAL BIOEQUIVALENCE STUDIES

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# Objectives

1. To remind us, this is a partnership.
2. To provide insight to a few challenges experienced by Industry in the conduct of complex Bioequivalence Clinical Studies.
3. To identify some opportunities to help circumvent the challenges of complex bioequivalent studies and advance generic products to market.

# Balancing Act

- Pipeline strategy
- Formulation & BE study methodology selection
- Increasing costs & complexity
- Patient access
- Speed & high growth markets
- Intellectual property & commercialization
- Prolonged & uncertain regulatory processes
- Data quality & extrapolation

# Increasing complexity in Clinical Trials

- Complex molecules/products
- Complex dual compounds
- Site of administration
- Variable performance of RLD
- Influence of excipients
- Evolving/Absent PSG's
- Limited data & publications
- Influence of technology
- Therapeutic BE & superiority
- Complex designs/endpoints
- Patient access & variability
- Rising costs
- Available API, RLD, method
- Protocol compliance
- Data collection & quality
- Drug blinding & packaging

# Challenges of Complex Metered Delivery Systems

## Challenges

- Multiple strengths & limited data
- High screen fail rates due to non-responders
- Intra-subject variability with inhalation products
- Variability in instrumentation & use
- Method challenges

## Opportunities

- Device comparison & performance
- Durability studies
- Alternative methodologies
- Change in device expectations

# Challenges of Complex Hormonal Products and TDS

## Challenges

- Cost and time
- Multiple application sites with similar absorption
- Transference/Washing studies
- Invitro apparatus not designed for patches
- Delay to market

## Opportunities

- Standardized procedures & objective measurements
  - Analytical standards
  - Pass/fail criteria for I&S studies
- Controlled communications in lieu of pre-development meeting

# Challenges of Complex Derm Corticosteroids

## Challenges

- Weak corticosteroids may pose blanching issues
- Irritating API's can also negate blanching
- DR data is not always reproducible in VCA pivotal BE studies
- Lot to lot variability in reference products

## Opportunities

- Evaluate collective data
  - Homogenous populations
  - Variable APIs
  - Blanching profiles
  - Dose response relationships
  - Occlusion
  - Failed VCA studies

# Challenges of Complex Topical Products

## Challenges

- Limited RLD availability
- PSG recommended endpoints past maximum efficacy
- Non-specific application amounts.

## Opportunities

- Characterization data on RLD from different regions
- Acceptability of reduced timepoints
- Measurable application amounts (ie. $cm^2$ )

# Placebo Challenges

## Challenges

- High placebo effects with marginally effective products
- Too unreliable for self-limiting conditions
- Enrollment challenges
- Increased deviations & lack of compliance
- Less value with highly effective products

## Opportunities

- Compare case studies where placebo is necessary or not & update PSGs

# Summary

- We share similar challenges & obligations.
- There are many barriers with complex bioequivalence studies and getting generic products to market but also opportunities.
- We can circumvent challenges through shared "value added data" and alternative data driven and science-based approaches for Bioequivalence.

*Resources: Opinions collected from Richard Stec, PhD, Jonathan Schwartz, Sethu Kavuri, PhD, Jocelyn Gruel-Clark, Journal of American Medical Association, Association of Accessible Medicines*