Relative Bioavailability: Pharmacodynamic and Non-Traditional Endpoints

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FDA SBIA Bioavailability Webinar – October 26, 2022

DISCLAIMER

THE OPINIONS PRESENTED ARE THE VIEWS OF THE PRESENTER AND SHOULD NOT BE CONSTRUED TO REPRESENT FDA VIEWS OR POLICY

Objectives

- Non-Traditional Endpoints
  - Partial AUCs
  - Point to Point Comparison
- Pharmacodynamics (PD) Endpoints
  - Pulmonary Product
  - Topical Product
- Clinical Endpoints
  - Topical Product

Approaches to Evaluate BA

- PK endpoints preferred
  - Most accurate, sensitive and reproducible endpoint
- PD if PK endpoint is not possible
  - Well justified PD endpoint

Approaches to Evaluate BA

- In Vitro Studies
  - e.g. In Vitro Dissolution
    - F2 comparison

- Comparative Clinical Studies
  - When measurement in an accessible biological fluid (PK approach) or PD approach is not possible
    - Least sensitive

Non-Traditional PK: Partial AUCs

- Certain class of drugs, Cmax and Total AUC may not be sufficient
  - Onset and Duration are critical
    - e.g. Complex dosage forms of ADHD drugs
    - e.g. Analgesic
- Time to truncate partial AUC should be related to a clinically relevant exposure measure
- Sufficient quantifiable samples should be collected to allow adequate estimation of the partial AUC.
- Consult Review Division

Example 1: New ER Formulation of Drug A

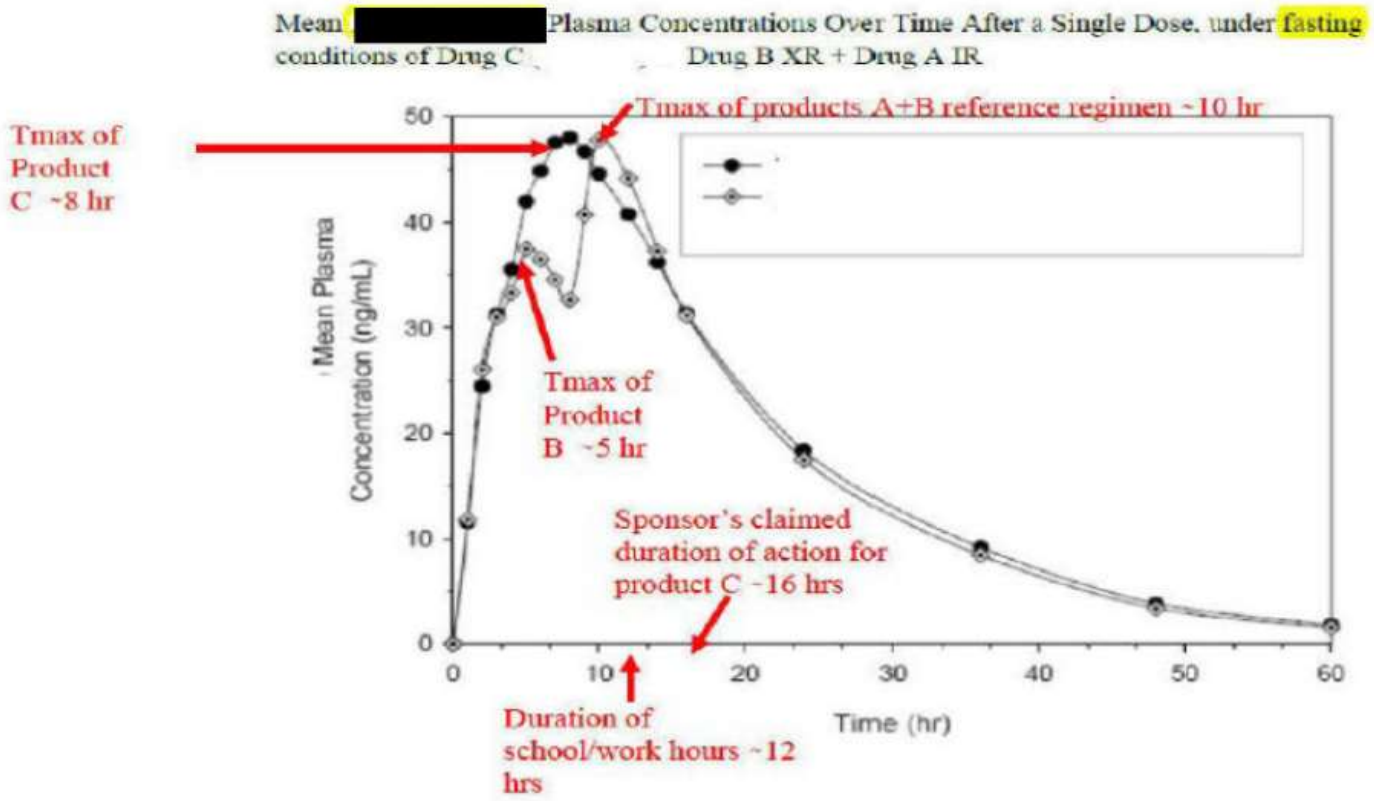
- **Drug A**
- Indication: Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (>18 yrs.), adolescents (13-17 years) and children (6-12 years)
  - Desired exposure profile: coverage during waking hours for patients to be productive at school or work but able to sleep at night
- **Product A**- immediate release (IR) dosage form of Drug A
- **Product B** – QD extended release (XR) dosage formulation of Drug A
    - Product B XR is intended to provide coverage up to 12 hours, however, physicians commonly prescribe an additional dose of Product A IR after 8 hours of Product B XR dose due to possible lack of effectiveness for the 12- hour intended duration .
- **Reference clinical regimen:** One dose of B XR in the morning + one dose of A IR 8 hours later

Example 1: New ER Formulation of Product B

- Test product:
  - **Product C**: QD, triple-bead, sustained-release formulation. Bead provides additional delayed release that is intended to provide symptomatic relief for up to 16 hours.

- Regulatory:
  - Applicant submitted product C via the 505(b)(2) pathway

BA study results (comparing Product C to Product B XR + Product A IR)



PK parameters for evaluation

What PK parameters would you recommend to the sponsor of Product C to evaluate in determining whether the two dosing regimens are equivalent?

In adults: Under both fed and fasted conditions

- Bioequivalence: Cmax, AUC0-last, AUC0-inf
- Therapeutic equivalence -> AUC0-5h (early onset of response), AUC5-12h (sustaining the response)

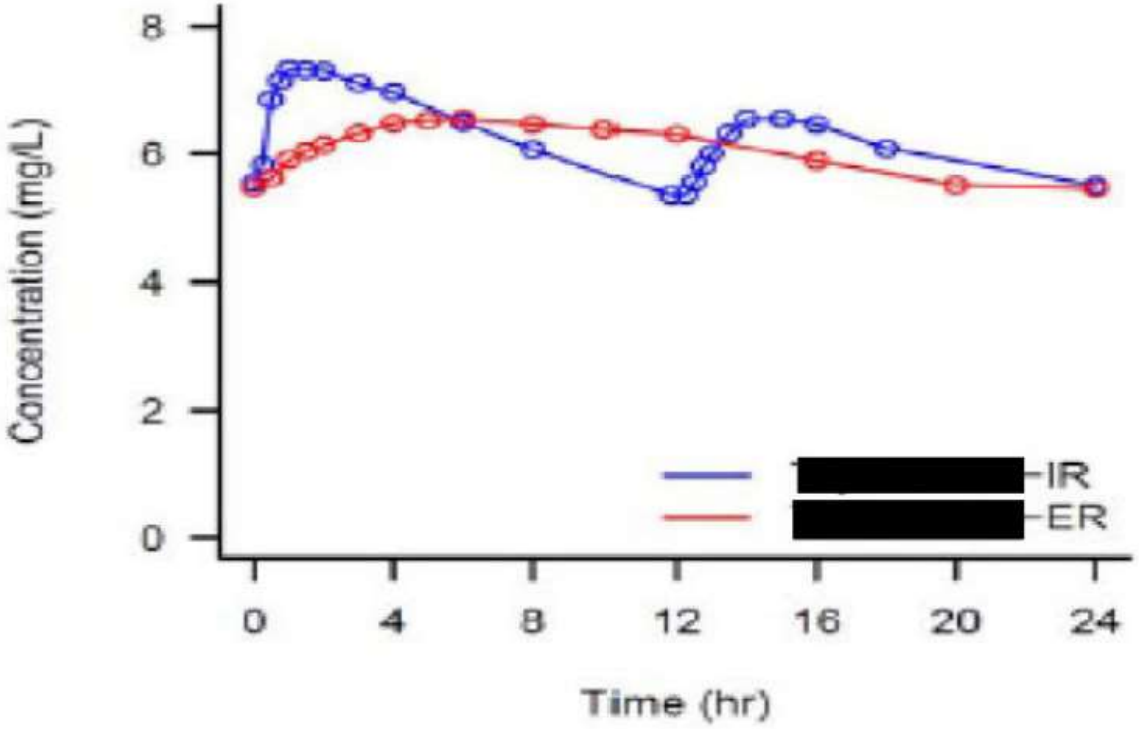
PK Parameters- Rationale

Parameter	Rationale
Cmax	Bioequivalence
AUC0-last	
AUC0-inf	
AUC 0-5	Early onset of response
AUC 5-12	Sustaining the response: based on school/work hours and Tmax of sustained release formulation
AUC 12-16	Maintenance of response: based on efficacy claim

Example 2: Product Y XR

- Drug Y
- Treatment of Epilepsy
- No safety and efficacy study
- 505(b)(2) Application
  - LD: Product Y IR
- PK exposure comparisons
  - AUC, Cmax, Cmin
  - E-R for Cmin
    - Reduction of seizures correlated to Cmin
  - Point to point concentration comparisons
  - Partial AUC comparison

Drug Y : XR (ER) vs IR

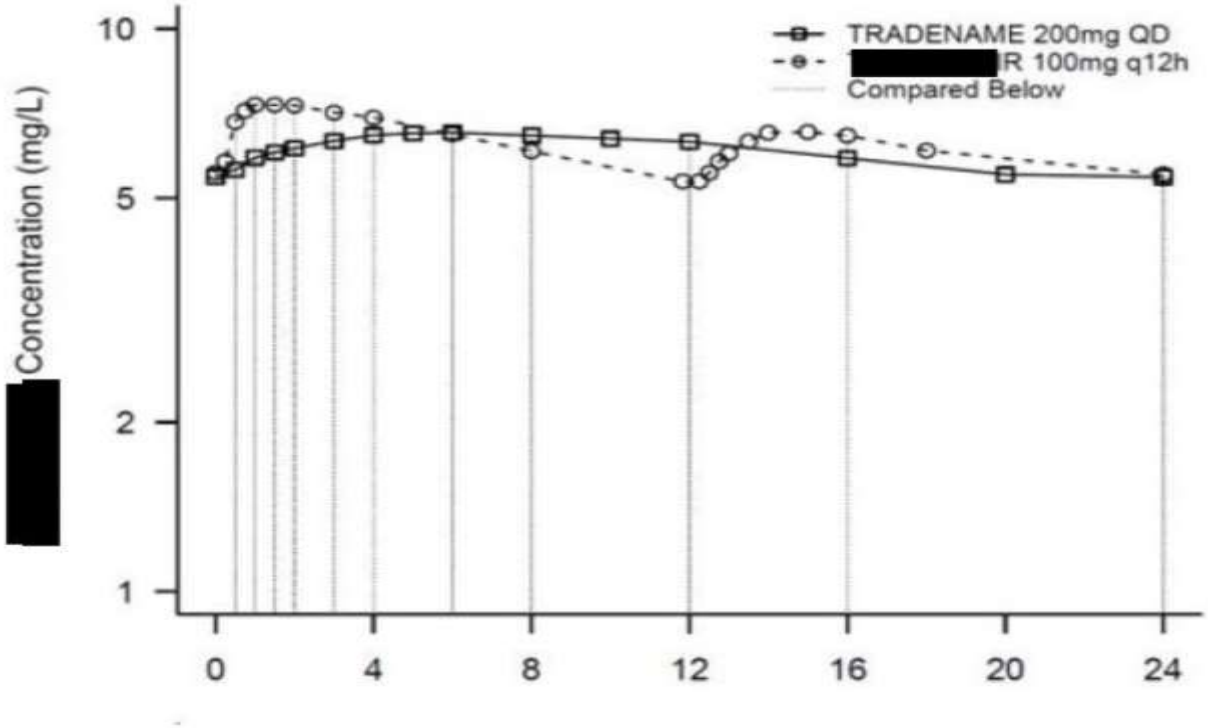


Drug Y: XR (A) vs IR (B)

[redacted] Summary of statistical analysis for relative bioavailability of 200-mg dose of [redacted] XR™ vs. [redacted]® at steady-state

Parameter	N	[redacted] XR™ (A) LS Mean	[redacted]® (B) LS Mean	Geometric Mean Ratio (A/B, %)	90% CI
AUC0–24 (ng·h/mL)	33	144000	149000	97.06	(94.01, 100.21)
Cmax,ss 0-24 (ng/mL)	33	6690	7600	88.01	(85.10, 91.02)
Cmin,ss (ng/mL)	33	5120	5130	99.91	(95.87, 104.13)

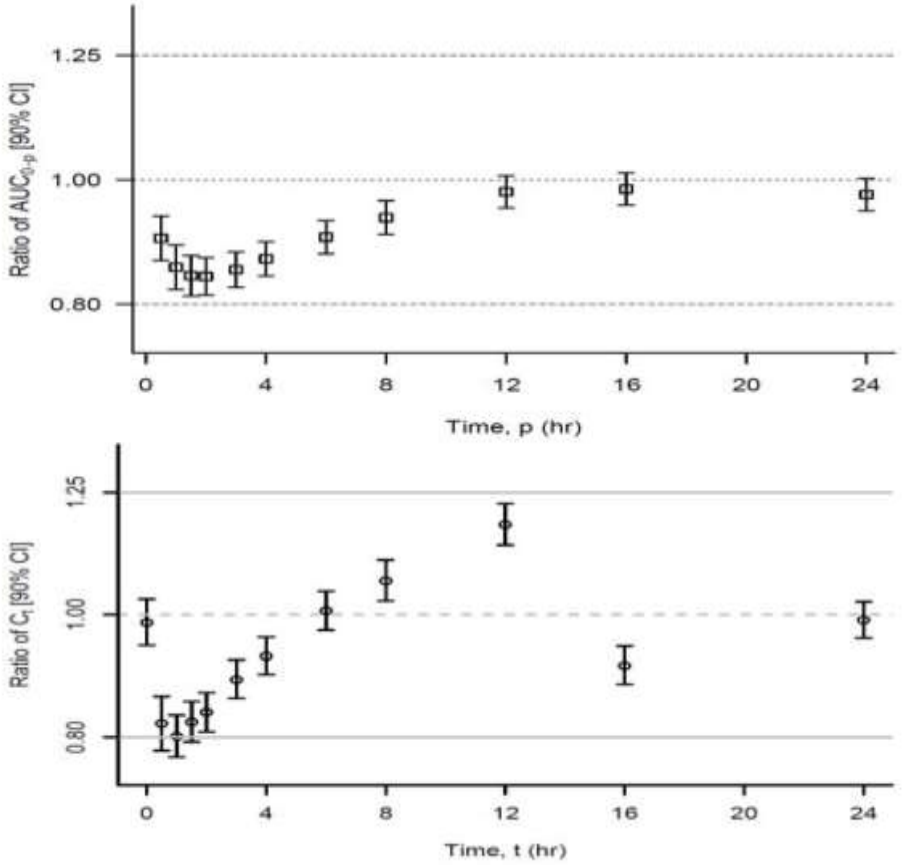
Drug Y XR vs IR: Point to Point Comparison



Analysis of point-to-point Drug Y concentrations after XR and IR administration

C_t	[redacted] Geometric LSM (mg/L)	[redacted] IR [redacted] Geometric LSM (mg/L)	Ratio (%) [redacted] / [redacted] IR	90% CI (%)
C_0	5.45	5.52	98.63	(94.57, 102.85)
$C_{0.5}$	5.61	6.83	82.03	(78.07, 86.19)
C_1	5.87	7.32	80.16	(77.14, 83.29)
$C_{1.5}$	6.01	7.30	82.32	(79.33, 85.41)
C_2	6.10	7.28	83.75	(80.81, 86.81)
C_3	6.29	7.07	88.94	(85.89, 92.10)
C_4	6.44	6.94	92.79	(89.68, 96.00)
C_6	6.51	6.46	100.73	(97.23, 104.36)
C_8	6.42	6.03	106.45	(102.54, 110.50)
C_{12}	6.28	5.32	117.95	(113.56, 122.51)
C_{16}	5.86	6.42	91.22	(88.12, 94.43)
C_{24}	5.44	5.49	99.04	(95.81, 102.39)
[redacted]				

Product Y XR vs IR: Point to Point Comparison



Pharmacodynamic (PD) Approaches

- PD endpoints with sufficient accuracy, sensitivity, and reproducibility
- Biomarker relevant to disease process
- Dose-response relationship demonstrated
- Consult Review Division

Examples: PD Approaches

- Albuterol metered dose inhaler
  - FEV
- Other inhalers
  - e.g. exhaled nitric oxide (inhaled corticosteroids)
- Topical Ointments and Creams
  - e.g. skin blanching (fluticasone propionate)

References

Hendeles L et al., The AAPS Journal, Vol 17, No. 3, May 2015

Zou, P et al and Yu, L, Pharmacodynamic Endpoint Bioequivalence Studies https://www.researchgate.net/publication/300023430_Pharmacodynamic_Endpoint_Bioequivalence_Studies

Clinical Studies: Topicals

- Topical delivery systems represent formulations that are intended to deliver drugs locally rather than systemically to treat local pathophysiologic conditions

Clinical Studies: Topicals

- Clinical study may be considered sufficient for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes.

21 CFR 320.24 (b)(2)

BA/BE Recommendations for Topical Products

- The trial itself could be a stand alone trial in phase II or could be a sub-group of subjects in a larger phase III trial. Either approach is reasonable.
- The sponsor should demonstrate that systemic exposure from their product under maximal usage condition is comparable to a comparator product so that systemic safety will also be comparable.
- If there is no comparator product, the systemic exposure should be evaluated in light of systemic adverse events.
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Additional Requirements for Topical Products

- Evaluation of the Vasoconstriction Activity of Topically Delivered Corticosteroids in Normal Skin in Healthy Adult Subjects can be the basis of potency ranking and BE of Corticosteroids.
- Agents having the potential to suppress Hypothalamus-Pituitary-Adrenal Axis should be tested for possible HPA Axis suppression.

Summary

- Non-traditional PK parameters may be needed for some disease conditions and complex drug products (e.g. Analgesics, complex ADHD drugs)
- Onset and duration important considerations
- pAUCs, point-point concentration comparison may be reasonable under certain scenarios

Summary

- PD endpoints reasonable when PK is not feasible
- Clinical studies allowed if PK or PD not possible (e.g. Topicals)
- Consult Review Division

Acknowledgment

- Mehul Mehta, Ph.D.
- Ramana Uppoor, Ph.D.
- Ta-Chen Wu, Ph.D.
- Angela Men, MD, Ph.D. (ex-FDA official)
- Johnny Lau, Ph.D.
- Tapash Ghosh, Ph.D.
- Dakshina Chilukuri, Ph.D.
- Jaya Vaidyanathan, Ph.D.
- Okpo Eradiri, Ph.D.
- Ethan Stier, Ph.D.
- Paul Seo, Ph.D.
- Members of BA Working Group

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Thank you!