



Regulatory perspective on the need and timing of clinical food effect studies

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DISCLAIMER

- Views expressed are mine and do not reflect official FDA Policy.

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- II. Need
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- IV. Labeling
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I. Acknowledgments

Ramana Uppoor

John Lazor

Brian Booth

Joe Grillo

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Need

Guidances:

1. Food Effect BA and Fed BE Studies guidance of December 2002
2. General BA/BE Guidance; March 2003
3. General BA and BE Guidance for INDs and NDAs; March 2014 Draft

Need

4. BE studies guidance for ANDAs:
 - December 2013 draft
 - Generic drugs are required to show fasted and fed BE to the RLD
 - Fed BE is not required only in case when the D&A section of RLD labeling states that the product should be taken only on an empty stomach
 - In-vivo BE studies are waived for BCS Class 1 products provided the generic product shows rapid and similar dissolution to the RLD

Need

Central Concepts:

- a) Generally, fasted single dose study in healthy subjects is most sensitive to detect impact of formulation differences
- b) The in-vivo FE study should be designed such that the worst-case scenario is tested
- c) It is critical to identify all the factors that contribute to the variability in systemic exposure of the studied drug; FE can be a major one.

Need

- d) There is a lot of very useful information available in the NDA database, e.g., nature and quantity of the excipients, properties of the drug substance (e.g., solubility, permeability, polymorphism, salt/base), manufacturing complexity, dissolution / release of the drug product, linear PK / dose proportionality over a wide dose range, that can resolve the need for additional FE studies

Need

Food Effect (FE) Characterization

- 1) Typically required for the following oral IR NDAs: NME, 505b2, a new dosage form, and a combination product
- 2) Required for a Modified Release dosage form NDA; to rule out dose-dumping
- 3) Typical meal is FDA high fat breakfast which is high-fat (50%), high-calorie (~1000) meal

Need

- 4) The rationale is that the high fat meal is the maximum-challenge / worst-case scenario for the dosage form.
- 5) May not be practical for patients with certain disease condition, e.g., Oncology; disease appropriate meal composition.
- 6) *When food increases BA and dosing requires the product to be taken with food, meals of differing compositions may need to be studied.*

Need

- 7) The typical food effect study is well powered.
- 8) If the effect is within the traditional BE limits of 80-125%, conclusion of 'no food effect' is drawn.
- 9) If not, effect of food on the rate and extent of BA, and its clinical relevance, are interpreted using the framework created using the exposure, efficacy and safety database provided in the NDA; *exceptions would be acute effect indications like pain.*

Need

- 10) Findings of the FE study lead to the appropriate statement(s) regarding the clinical relevance of the food effect in the Innovator product label.
- 11) How the drug product was dosed, with regard to meal timing, in the phase 3 program for the innovator product can also inform clinical relevance of the food effect.

Need

Predicting FE:

12) BCS approach: BCS Class 1 products, i.e., products with HS, HP and rapid dissolution, that show high F , F_a under fasting conditions are unlikely to show FE

Need

Combination Products:

13) IR only: if the combo is BE under fasted conditions to individual drugs given together, FE maybe extrapolatable; case can be made based on NDA knowledgebase.

14) Need for FE characterization in case of an IR + MR combination product? would be the same as an MR product. Even if the IR drug FE is characterized, waiver of FE characterization for combination with an MR component would be difficult.

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Timing

- 1) BCS, pre-clinical, in-silico, etc., approaches can provide the signal about potential food effect prior to the initiation of clinical program.
- 2) Fed / fasted condition can play a critical role in optimizing dosing for the pivotal efficacy trial; FE characterization should be done by this stage.
- 3) On a rare occasion, the entire drug development is done under fed conditions, including the pivotal efficacy trials with the labeling stating that the product has to be taken under fed conditions.

Timing

- 4) For IR products, a case can be made for not repeating FE study in late development based on the knowledgebase developed for the NDA (central concept 4).
- 5) For MR products, it is difficult to extrapolate FE in case of a significant formulation change; FE should be known of the TBM dosage form.

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Labeling

- ‘Effect of Food’ subheading in Section 12.3
Pharmacokinetics:
 - A description of the food(s) or meal(s) used with respect to total calories and composition (fat, carbohydrate, and protein content) should be stated.
 - Specific study results, such as the effect of food on important PK parameters should be included.
 - If studies are conducted to assess the effect of the timing of meals on absorption, those study results should be included.

OUTLINE

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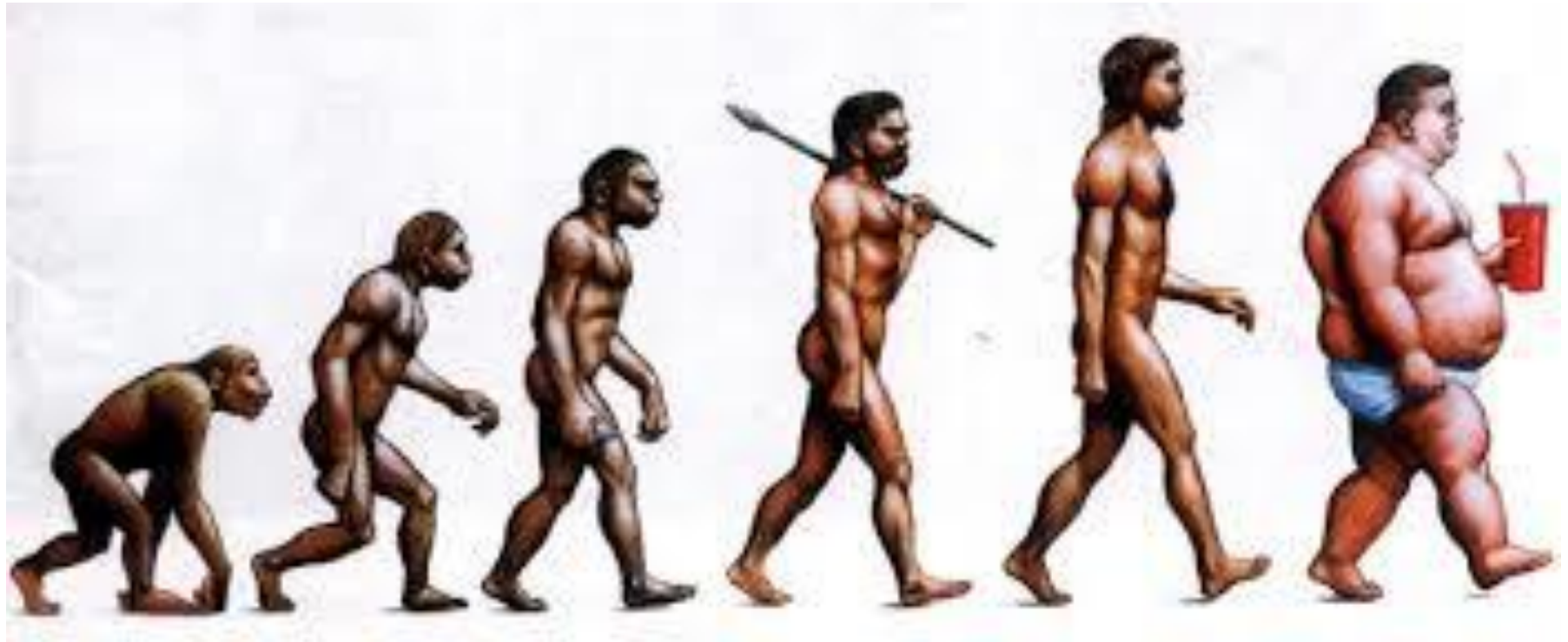
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Example

Avidri example (From Pink Sheet of 9/10/15):

- Oxycodone IR with abuse-deterrent properties
- Intended to be dosed every 4 to 6 hours
- Opioids are generally taken without regard to food
- *Significant FE – 27% lower C_{max}, also, median T_{max} in presence of food was about four hours for Avidri compared to 1.5 hours for Roxicodone.*

Example

- “it is not clear whether labeling would be sufficient to change longstanding behaviors of both prescribers and patients.”
- “All of these issues may result in patients taking Avidri without regard to food, leading to variability in systemic exposure to oxycodone, variable or delayed efficacy, and the possibility of taking extra doses that could lead to serious adverse events.”
- The joint AC (Anesthetic and Analgesic Drug Products + Drug Safety and Risk Management) voted 24 to 1 against approval.

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Summary

1. FE study is expected for all oral IR NMEs, 505(b)(2), new dosage form, combination product, and MR NDAs; depending upon the drug and dosage form characteristics, FE can be a critical factor in optimizing pivotal efficacy trials
2. High fat, high calorie (“FDA Breakfast”) is generally the meal of choice.
3. Results from this study, as well as other relevant information, lead to statement(s) regarding the effect of food on BA in the innovator product label.

Summary

4. Utilize all the available information in your NDA database, e.g., nature and quantity of the excipients, properties of the drug substance (e.g., solubility, permeability, polymorphism, salt/base), manufacturing complexity, dissolution / release of the drug product, linear PK / dose proportionality, to address the need for the food effect characterization of your product



Thanks!!