Your Generics & Biosimilars Industry

Reducing the Burden of Proof – Re-evaluating the Necessity of Fed Bioequivalence Studies

May 1, 2019

Fed BE Studies for ANDA Products Submitted to FDA

- As established in the 2002 FDA guidance on Food-Effect Bioavailability and Fed BE Studies, the majority of drug products must have PK BE studies submitted under fasting and fed conditions.
- This requirement is even mandated when the labeling of the drug product specifically states, “take on an empty stomach” (absent any safety concerns)
- This places an enormous burden on industry, and we believe relief is possible.

Fed BE studies for ANDA Products Submitted to FDA

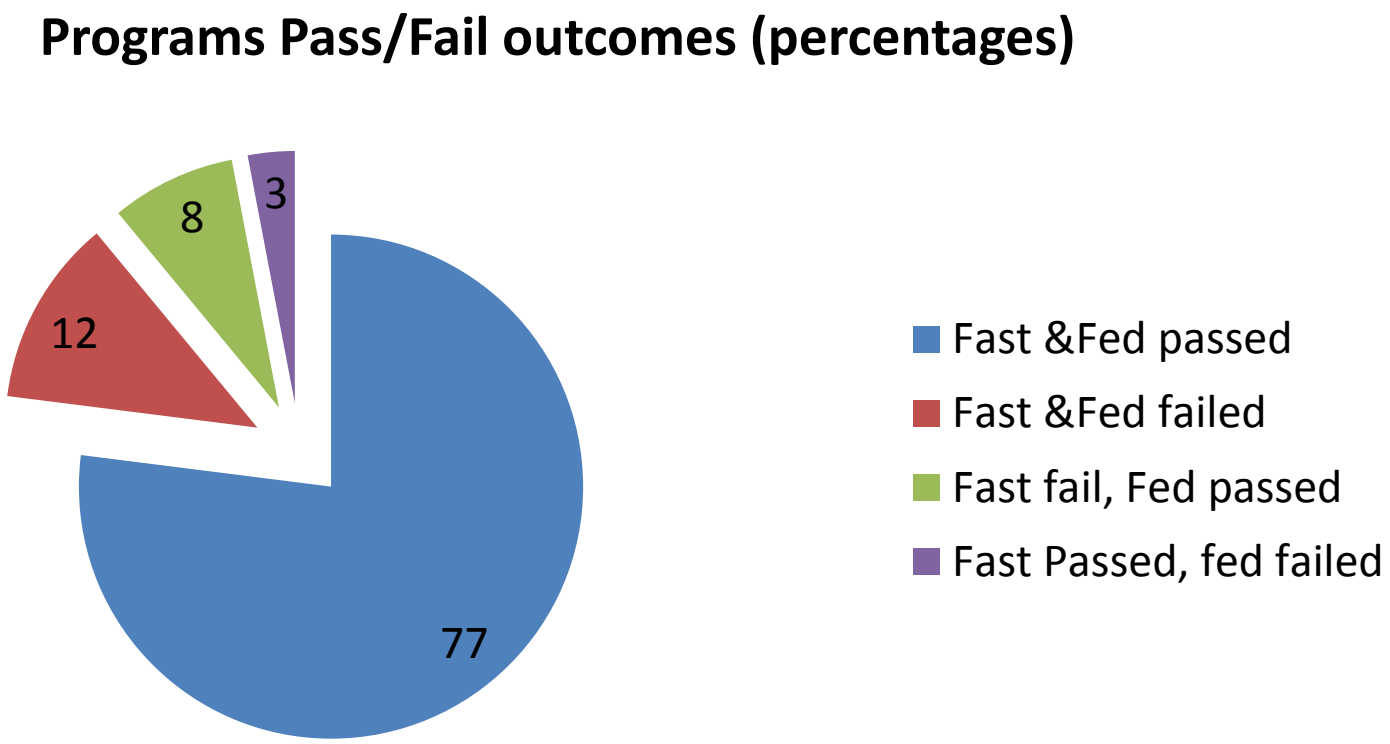
- Clearly, the dosage form, formulation of drug product, solubility and permeability of the drug substance could have an effect on the PK of a product under fed conditions.
- While we see the clear need for studies under fed conditions for modified release (MR) products labelled to be taken under this condition, we believe a more simplistic approach for immediate release (IR) products is warranted.

Current Health Authority Requirements

US Fed Study Requirements	EU Fed Study Requirements	Canada Fed Study Requirements	Australia Fed Study Requirements
Fed studies conducted on all solid oral dosage forms, unless safety is a concern	Fed studies are generally not needed for IR products, unless the SMPC states to dose only with food (in which case these products do not have to conduct require a fasting study).	Similar to EU	Similar to EU

Insight Into Generic Industry Statistics

- Apotex, Mylan and Teva took a representative sample of all immediate release product programs conducted at the three companies (n= >400).
- Categorized programs by Pass/Fail outcomes based on Fasting and Fed study results on same formulation (batch).



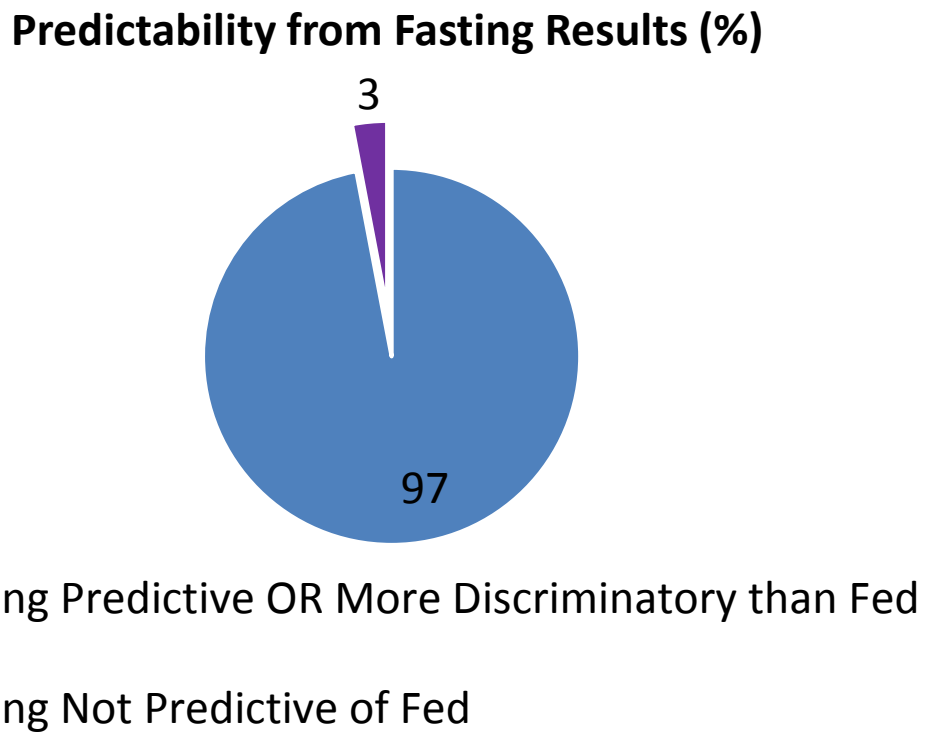
Insight Into Generic Industry Statistics

- Collapsing the categories into meaningful outcomes yields 2 important categories:

Fasting Predictive <u>OR</u> More Discriminatory than Fed	**Fasting Not Predictive of Fed**
Fast & Fed Pass	Fast Pass & Fed Fail
Fast & Fed Fail	
Fast Fail & Fed Pass	

Fed Study is **<u>not</u>** informative >95%

Fed Study **<u>is</u>** informative <5%



Observed Trends

- For almost all immediate release BCS class I compounds, food effects are minimal. In our experience, a vast majority of the fed BE studies on this class of compound pass, if the corresponding fasting study has passed. Additionally, FDA has already accepted that biowaivers can be applied for this class of product.

- The same is true of BCS class III compounds, in our experience, typically, the food effect is negative, but a vast majority pass if the corresponding fasting study passed.

- For BCS class II compounds (specifically weak acids and bases with high pKa), those food effects are most often positive and pass if the corresponding fasting study has passed.

- Class IV compounds are the anomaly. There are numerous instances where fasting and food studies have shown marked differences, where the fasting study outcome is not predictive of food effect study outcome and vice versa.

Expansion Into Elimination of Sprinkled on Soft-food Studies

- Referring to instances only when sprinkling contents of a capsule onto applesauce and/or yogurt. Not referring to instances where crush or disintegrate and then place on a food.

- If passing fasting BE studies, our experience shows that one is going to pass an applesauce or administration into soft food (i.e. yogurt) study assuming in vitro stability of the product in that media for a certain length of time has been assured.

- Other regions not requiring this type of study, and instead rely on in vitro data.

Summary and Suggestions

- From the overall generic industry statistics trend data:
  - The vast majority of programs (>95% cases) demonstrate non-informative fed BE results. That is, the fasting study alone can predict or better discriminate PK results than the fed.
  - Where the fasting study passed and the fed study failed (<5% cases), the IR products were most often poorly soluble.
- We have the following suggestions:
  - FDA should adopt requirements similar to EU and other regions: Fasting study only for IR products.
  - The label should be paramount; if the product is labeled to be taken only under fasting conditions, no fed study should be required. Products labelled to be taken with or without meals should study the most predictive condition (fasting).
    - While we focused the discussion on IR products, this can be expanded to MR products where labeled administration instructions should dictate BE requirements.
  - If fed studies are needed, it should be limited to certain low solubility IR products (i.e. those that pose a patient risk to safety or efficacy if BE is not assured under fed condition).
  - The need for sprinkle studies of IR products should be waived, on the basis of assurance of in vitro product contents stability.

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Thank You