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Potential Role of Bayesian and PBPK Approaches to Generic Drug Approval

Joga Gobburu PhD FCP MBA

Professor, School of Pharmacy

University of Maryland

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Premise

- Currently for certain products an efficacy study is required to support an ANDA. For these products, drug exposures cannot be measured or the systemic levels are deemed not reflective of the local bioavailability.
- Several of such products do not have generics today; as the clinical studies turn out to be negative or uninterpretable owing to the nature of the endpoint, patient population or non-inferiority testing.
- It is generally accepted that drug levels are more sensitive than clinical endpoints to identify true differences.

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Premise

- Let us consider two cases:
  - Systemic levels cannot be measured (or no consensus on their relevance).
  - Systemic levels can be measured.

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Systemic Levels Cannot be Measured

- Current a frequentist approach is recommended for these clinical trials. Given that generics or enough generics are not approved for certain products, there is clearly a need to consider alternative approaches without compromising the efficacy/safety.
- It is to be noted that for the brand, the comparison might have been with placebo; for generic the comparison is with the brand (and placebo). Making the generic trial 3x larger than the brand trial – against the spirit of the generic rule.
- Bayesian approach makes particular sense in this case, as there is indeed good quality prior information about the efficacy/safety from the brand.
- The placebo data and the double-delta of the brand from the brand trials and other sources can form the prior with a measured certainty. Various options for the trial size for the generic can then be explored. Because there will be a good reliance on the prior data; the trial size for the generic ought to be smaller. The hope is that this novel approach will encourage more sponsors to develop a generic.

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Systemic Levels Can be Measured

- There are attempts to develop a PBPK model to quantify the local bioavailability (rate and extent) for products. Conceptually, the goal is to develop, validate and apply the PBPK model to compare the local exposures of the brand and generic products to support the ANDA. Of course, there are other sources of data that also contribute to the application.
- For every sponsor to develop, validate and apply the PBPK model is impractical.
- Even for those who can do it, having good quality data pertaining to the various physiologic processes especially from human subjects is not practical.
- So the point is the playing field is not even…
- The proposal, hence, is for FDA to invest is developing these PBPK models (thr various mechanisms), validate. Once the PBPK model is validated:
  - There could be specifications for certain in vitro experiments which when met could form the basis for the generic evaluation.
  - In cases where PBPK is not definitive, but has increased the reliance on the relationship between the local and systemic exposures; the bioequivalence testing can be performed used systemic levels directly without the need for further use of the PBPK model.