Is there a Potential to Apply the Bayesian Approach in Generic Drug Development and Approval?

A Provocation

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Generic Drug Approval *already* employs a Bayesian-*like* Approval Approach

What is Bayesian Approach?

How is a *Bayesian-like* Approval Approach being employed in Generic Drug Approval?
Bayesian Approach

**Bayes Theorem:** Prior prob \times Likelihood = Posterior prob

- **Historical Data**
- **Experiments & studies**
- **Expert Knowledge**
- **Probability of Hypothesis from extant data**

\[ P(	ext{Hypothesis}) \times P(	ext{New Data} | \text{Hypothesis}) = P(	ext{New Data}) \]

\( X \rightarrow + \rightarrow \)

Updated Probability of Hypothesis

\( \Rightarrow \) Decision

UCSF-ACDRS 2017
**Bayesian-like Approach employed in Generic Drug Approval**

**Bayesian-like Approach:** Extant knowledge ‘+’ PK → BE

- **Bioequivalence trial data**
- **Two 1-sided test Result**

- **‘Prior’**
- **‘Likelihood’**
- **‘Posterior’**

Therapeutic Equivalence?  

“Bio Drift”???
Is there potential to formally employ Bayesian approaches?

A little History

Opportunities to streamline generic DD&RA
A Little History

• **1970’s: Bioavailability, equivalence**
  – Frequentist “Power” approach\(^1\) \(\Rightarrow H_0: AUC_{\text{Gen}} = AUC_{\text{Ref}} \) @ \(\alpha = 0.05\), Power 80%
  – Non-parametric “75/75, 75/125 rule”\(^3\)

• **1980’s: Problems with Power and ”75/75, 75/125” approaches**
  – Highly variable drugs – low statistical power
  – Weak performance characteristics and lack of rigorous statistical foundation

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1 Nat. Acad. Sci ’71
2 Westlake ’76
3 Harter, Cabana, FDA ~ ’80; Hayes ‘81

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A Little More History

• **80’s: Replacing the Power and 75/125 approaches**
  
  – Bayesian proposals
    
    • Rodda ‘80, Selwyn ‘81: post-Bayes *point prob* of $\text{Diff}_{\text{bio}}'$s $> +/\text{- }20\%_{\text{ref}}$ @ non-informative priors (t-dist, Jeffreys) & data Normally Distributed
    
    • Mandallaz ‘81, Fluehler ‘83: post-Bayes *prob distributions* $\text{Diff}_{\text{bio}}'$s $< +/\text{- }20\%_{\text{ref}}$ @ non-informative prior
    
    • Selwyn ’84: extension of Selwyn ‘81 to *complex trial designs* & Jeffreys prior

• **1987 Frequentists Win! – “Two One-Sided t-test Procedure” (Schuirmann ’87, Westlake ’76)**
  
  – $H_{01,02}: \text{AUC}_{\text{Gen}} - \text{AUC}_{\text{Ref}} < 0.8 \& >1.2$ @ $\alpha = 0.05$, Power 80%

• **More proposals of Bayesian approach**
  
  – Grieve ‘85, Radcine-Poon ‘87, Ghosh ’03, ’07’, ’08 (carryover effect, 2-stage procedure, Bayes Factor approach, multivariate outcomes
  
  – Longford ‘16: *Bayesian Decision Theory*
Opportunities to streamline generic DD&RA

• Incorporation of prior knowledge
  – Evaluation of “bio drift”
    • Informative prior based on bio of reference product @ NDA Approval
  – Bayesian adaptive generic drug learning trial designs
    • 2-stage procedure of Raccine-Poon
      – No penalty for multiple tests or protocol changes
  – Bayesian Multivariate Bioequivalence of Cmax and AUC
  – Bayesian inference for regulatory review
    • Bayesian Decision Analysis

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Opportunities to streamline generic DD&RA

• New Guidances
  – That Teach (e.g. CDRH Bayesian Methods)
    • Bayesian methods applied to generic drug development and approval

• Education
  – Bayesian inference, Evidence Assessment, Decision Analysis

• Research
  – “bio drift”
  – form of ‘prior’ distribution
  – estimation vs hypothesis testing for approval & labeling

Carl Peck 2014
END