FDA Workshop
Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
Day 2 am Session: Emerging Quantitative Methodologies and Their Use in Product Lifecycle Management
October 3, 2017, Washington DC,

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

A Provocation

Carl Peck

UCSF, NDA Partners

University of California
San Francisco
UCSF
School of Pharmacy

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

Historical Data

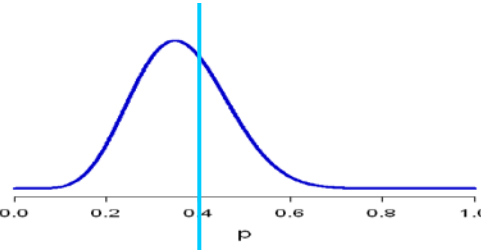
Experiments & studies

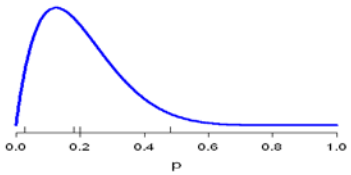
Expert Knowledge

Bayes Theorem: **Prior prob x Likelihood = Posterior prob**

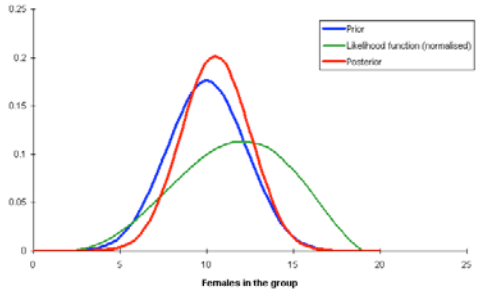
Probability of Hypothesis from extant data *x* ***New Data*** = ***Updated Probability of Hypothesis*** ⇒ ***Decision***

'Prior' ***'Likelihood'*** ***'Posterior'***

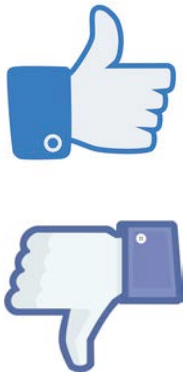




=



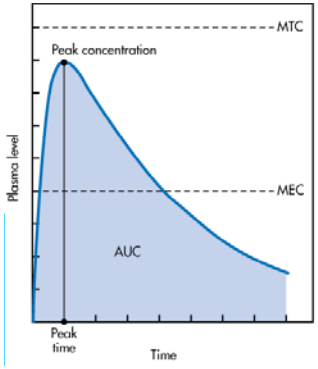
⇒



Bayesian-like Approach *employed in Generic Drug Approval*

Effectiveness & Safety of Approved Reference Product

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



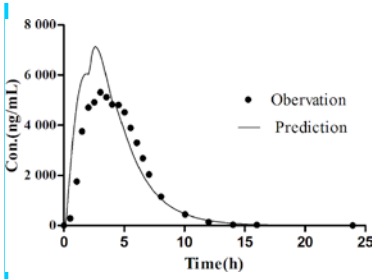
'+' ***Bioequivalance trial data*** **=** **Two 1-sided test Result** **=>**

'Prior' ***'Likelihood'*** ***'Posterior'***

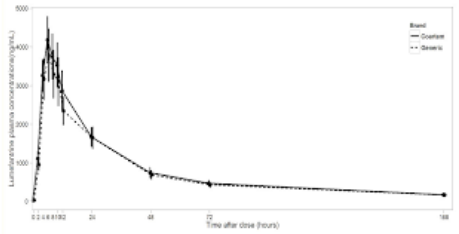
Therapeutic Equivalence ?

…..

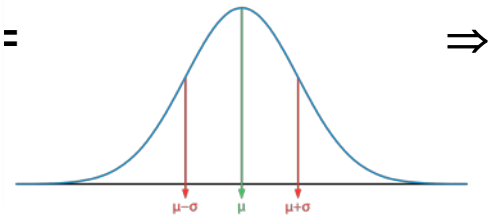
"Bio Drift"???



+



=



⇒

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]** => H_0: $AUC_{Gen} = AUC_{Ref}$ @ α = 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

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

A Little More History

- **80's**: ***Replacing the Power and 75/125 approaches***
  - **Bayesian proposals**
    - Rodda '80, Selwyn '81: post-Bayes ***point prob*** of $Diff_{bio's}$ **>** +/- $20\%_{ref}$ @ non-informative priors (t-dist, Jeffreys) & data Normally Distributed
    - Mandallaz ' 81, Fluehler '83: post-Bayes ***prob distributions*** $Diff_{bio's}$ **<** +/- $20\%_{ref}$ @ 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)***
  - $H_{01,02}$: AUC_{Gen}- AUC_{Ref} < 0.8 & >1.2 @ α = 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*

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

END