Bayesian methods and thinking in Pfizer’s PharmaTherapeutics Division.

How we got here, what we’ve done and where we’re headed.

Phil Woodward
VP Global Head of BioTherapeutics Statistics, Pfizer
Summary

• How did change come about?
• How it was actively managed
• Education, training and software
• What are we doing?
• The future?
How did change come about?

• Dissatisfaction with the current way of working
  – Usual issues with convoluted explanations of classical methods
  – Desire by all to interpret results as if they were Bayesian
  – Unsatisfactory approach to current use of Bayesian methods

• Vision of how things can be better
  – If we want Bayesian interpretation than let’s be Bayesian!
  – Benefits of formally incorporating prior knowledge
  – Ability to directly tackle the questions of interest

• Pragmatic and strong focus on benefits to the Business
  – Why should others support and join us to make these changes?
  – What are the immediate tangible benefits? Gain momentum.
  – What will be the longer term benefits? Prepare groundwork.
How did change come about?

• Someone with the authority & passion to bring about change
  – Head of Statistics supporting projects up to Proof-of-Concept
  – Backed up by a manager with the same vision
  – Colleagues enthusiastic by the challenge to make these changes
  – Allies in partner lines, e.g. Clinical Pharmacology, Clinical

• Willingness to take risks
  – Make changes without having all potential issues worked out
  – Leader has the backs of the colleagues implementing changes
  – Belief that things will be better by making the changes

• Address the major obstacles to successful implementation
  – Education, training & software
  – Expertise and experience to “hold the hand” of “Bayesian virgins”
  – Pragmatic approximate methods to minimise delays in getting started
Include in Departmental Goals

A default position of utilising Bayesian methods in all PoM and PoC studies, at least, unless there is good reason not to do so.

... informative priors to reduce the number needed on placebo, and perhaps, standard-of-care

... interim analyses based either on predictive probability of success or failure at the end of the study, or the current posterior probability that the effect size criteria have been met

... additional exploratory use of credible informative priors for the treatment effect
Informative Priors Guidance

Guidance Document produced

1. Select relevant historical data to derive prior
2. Formulate model to relate historical studies to new study
3. Calculate “effective N” given by informative prior
4. Build checks for prior misspecification into analysis
5. Document prior derivation
Typically (b) adequate, maybe with more complexity.

Typically,
\[ y_h \sim N(\theta_h, \sigma_h^2) \]

Exchangeable
\[ \theta, \theta_h \sim N(\mu, \tau^2) \]

(a) \( \tau = \infty, \mu = K \)
(b) \( \tau \sim \text{dist.} \)
(f) \( \tau = 0, \mu = \theta \)

(c) \( \theta_h = \theta + \delta_h \)
\[ \delta_h \sim N(0, \sigma_{\delta h}^2) \]
\[ \theta_h \sim N(\theta, \sigma_{\delta h}^2) \]
The derivation of the informative prior should be documented in a technical report that is stored along with the source data.

The report should contain the following information:

- Study background and objectives
- List of studies used to build prior
- Criteria used to select these studies
- Model used to relate historical studies to new study
- Prior details (i.e. mean and standard deviation)
- Description/model of how the prior will be used
Bayes Limited Duration Team Objectives

• Review and critique the current proposal
  – Ensure aims & benefits are clear
  – Identify issues with achieving these aims
  – Help identify what, if anything, should be mandatory or consistent
    • Consider trade-off between ease of communicating each project with need for flexibility of methods.
  – Help define and structure the goal to maximise wider engagement & impact

• Plan and assist with implementation
  – How should we address issues raised in 1b?
  – Who are the pioneers – PoC & large PoM studies?
  – Determine and help develop training, software, “self-help buddies”
    • Do we need external expertise to assist?

• Have our preferred way of incorporating Bayesian methods in operation within PTx
Education, Training & Software

- How is Bayes different? Why should we bother?
- Review theory, but with focus on implementation.
  - It is in our goals now!
- Win/OpenBUGS
  - BugsXLA
- SAS PROC MCMC
- R Scripts for study design operating characteristics
- Pragmatic approximations
How does Bayes add value? (statistical audience)

• **Informative Prior**
  – Natural approach for incorporating information already available
  – Smaller, cheaper, quicker and more ethical studies
  – More precise estimates and more reliable decisions
  – Sometimes weakly informative priors can overcome model fitting failure

• **Probability as a “degree of belief”**
  – Quantifies our uncertainty in any unknown quantity or event
  – Answers questions of direct scientific interest
    • \( P(\text{state of world} \mid \text{data}) \) rather than \( P(\text{data*} \mid \text{state of world}) \)

• **Model building and making inferences**
  – Nuisance parameters no longer a “nuisance”
  – Random effects, non-linear terms, complex models all handled better
  – Functions of parameters estimated with ease
  – Predictions and decision analysis follow naturally
  – Transparency in assumptions

• **Beauty in its simplicity!**
  – \( p(\theta \mid x) = p(x \mid \theta) \cdot p(\theta) / p(x) \)
  – Avoids issue of identifying “best” estimators and their sampling properties
  – More time spent addressing issues of direct scientific relevance
BugsXLA
Quick access to the power of Win/OpenBUGS
Consider a generic decision criterion of the form

\[ \text{GO decision if } \Pr(\delta \geq \Delta) > \pi \]

\(\delta\) is the treatment effect

\(\Delta\) is an effect size of interest

\(\pi\) is the probability required to make a positive decision

A Bayesian analogy to significance could be

\[ \Pr(\delta > 0) > 0.95 \]
Bayesian Study Design (Assurance)

Plot comparing classical ('conditional power') OC and assurance

- N.grp: 50  sigma: 5  pred prob: 0.83
- N.grp: 20  sigma: 5  pred prob: 0.57
- N.grp: 50  sigma: 15  pred prob: 0.27
- N.grp: 20  sigma: 15  pred prob: 0.15

Probability of GO decision (Power)

p(delta)

True value of delta

δ₀

ω
Worked example

Suppose predictive distribution (placebo prior)
\[ p(\gamma) \sim N(18, 12^2) \]

Forecast residual standard deviation
(obtained in usual way, not shown here)
\[ \sigma = 70 \]

Effective N of placebo prior
\[ \text{Eff.}N = (70 / 12)^2 = 34 \]
Unless no doubts at all, use Robust Prior
i.e. a mixture of informative and vague prior distributions
\[ p(\text{placebo mean}) \sim 0.9 \times N(18, 12^2) + 0.1 \times N(18, 120^2) \]

Represents 10% chance meta-data not exchangeable in which case, will effectively revert to vague prior (can also be thought of as heavy tailed distribution)

Also compute Bayesian p-value of data-prior compatibility
\[ \Pr(\text{“} > \text{observed mean} \text{”} \mid \text{prior} \sim N(18, 12^2)) \]

Note: predictive dist. for obs. mean \( \sim N(18, 12^2 + \sigma^2/n_p) \)
Diabetic Nephropathy PoC

- Expert elicitation and consistent with the literature
  - 632 placebo subjects in two large studies
  - Uncertainty in similarity with planned study accounted for
- Bayesian approach used this information in PoC study
  - Prior knowledge of placebo response equivalent to 100 subjects
  - Study completed 12 months sooner and with >$5M saving

![Graph showing prior for placebo response](image)

*Probability density vs. 12 week response/ baseline*
Diabetic Nephropathy Biomarker

Were the observed placebo data consistent with the prior?

Yes!

An informative prior appropriately down weights “extreme” observations.

Also ran an identical study with a different compound.

Yes again!
Parkinson's Disease Off-time

- Utilised 6 recent PD L-Dopa studies
  - 707 placebo subjects in total: 2008-2013
- Bayesian approach uses this information in planned study
  - Prior knowledge of placebo response equivalent to 53 subjects
  - Expected to save ~3 months and >$2M

![Meta-Analysis Data and Derived Prior](chart.png)
Bayesian Interim Analysis
(Interim analysis predictive probability)

Plot comparing ‘conditional power’ and predictive probability following interim analysis (25/grp), vague prior distribution

Only differences to analysis done prior to study start are:

1) OC curve conditional on both delta and interim data
2) ‘Belief distribution’ for delta updated using interim data

Prior or Posterior depends on one’s perspective (‘Belief Distribution’)

could use informative design prior, updated using interim data …
Pragmatic Approximations
Predictive probability of end of study success at an interim.

End of study success criterion:
\[ \Pr(\delta > \Delta) > \pi \]

Data at the Interim (vague priors):
- \( M_I \) = mean estimate of \( \delta \) at the interim (sometimes the ML estimate);
  approximates the posterior mean of \( \delta \) at the interim
- \( V_I \) = variance of \( M_I \) (sometimes the squared standard error of \( M_I \));
  approximates the posterior variance of \( \delta \) at the interim

\[
1 - \Phi \left( \sqrt{\frac{V_U}{V_I}} \left( z_\pi - \frac{(M_I - \Delta)}{\sqrt{V_E}} \right) \right)
\]

When we have exactly half the information at the interim, this simplifies:
\[
1 - \Phi \left( z_\pi - \frac{(M_I - \Delta)}{\sqrt{V_I/2}} \right)
\]
Bayesian Emax Model

\[ E_0 + \frac{E_{max} X^\lambda}{ED_{50}^\lambda + X^\lambda} \]

\( \lambda \) sometimes referred to as ‘Hill slope’

when \( \lambda = 1 \) need ~80 fold range to cover ED_{10} to ED_{90}
Convergence issues are common with MLE of Emax models

Hill slope not restrained

Hill slope = 1

Most clinical data more variable than this and smaller dose range
Classical fitting algorithms can fail to provide any solution
Utilise prior from other relevant studies to avoid these two extremes
The Future? A more realistic “Discovery/ED prior”? 

Probability that mechanism is not relevant or a “PK/PD failure”

25% chance effect > Target Value

Positive PoC
Summary

• How did change come about?
  – Vision & determination by leader with authority to implement
  – Colleagues able and enthusiastic to make it happen

• How it was actively managed
  – Goals, documentation and strong advocate at Technical Reviews

• Education, training and software
  – Statisticians and scientific colleagues and other stakeholders

• What are we doing?
  – Bayesian:
    Study Design & Reporting, Interim Analyses, Complex Modelling

• The future?
  – Greater use of informative priors: “beyond MA of past studies”
  – Better decision making