Probabilistic Modeling to Support and Facilitate Decision Making in Early Drug Development

Huybert Groenendaal, MSc., PhD, MBA
EpiX Analytics

www.epixanalytics.com

EpiX Analytics

1. Specialized risk analysis and modeling
   (formerly called Vose Consulting)

2. Consulting, training and research

3. Clients in a wide range of industries:
   - Pharma
   - Mining
   - Manufacturing
   - Transportation
   - Financial industry
   - Animal health
   - Oil & gas
   - Many others

Early Drug Development:

1. First-in-human – Phase IIb
2. Decisions include:
   - Designing trials
   - Optimal dose and or dose regimes decisions
   - Make progress and terminations decisions

Early Drug Development – what we look at?

1. Efficacy – the desired effect and it's size
2. Clinical safety / Toxicology – undesired effects
3. Competitors – Compared to new drug, how 'good' will our drug be?
4. Regulatory – e.g. dose restrictions or other constraints

As well as other aspects….

What is the challenge?

1. Situations are complex, and incorrect progress and termination decision very costly;

1. Decisions often taken by ‘teams’;

2. Time = money

3. Even after collecting data (clinical trials etc.), often high amount of uncertainty. Often conflicting data.

Probabilistic modeling:

1. Sole goal is improving decision-making;
2. Can be used as part of model-based drug development (MBDD);
3. Nothing truly ‘new’ in terms of methodologies;
4. Often performed using Monte Carlo simulation

Probabilistic modeling – why?

1. Flexible in combining multiple sources of dissimilar information (Monte Carlo helps avoid difficult math)

2. Take into account uncertainty & variability simultaneously (including correlations)

3. Changes the questions decision-makers can ask, forces to think in 'ranges' and probabilities;

4. Fast, efficient and easy to access

Benefit 1. Combining multiple sources of dissimilar information

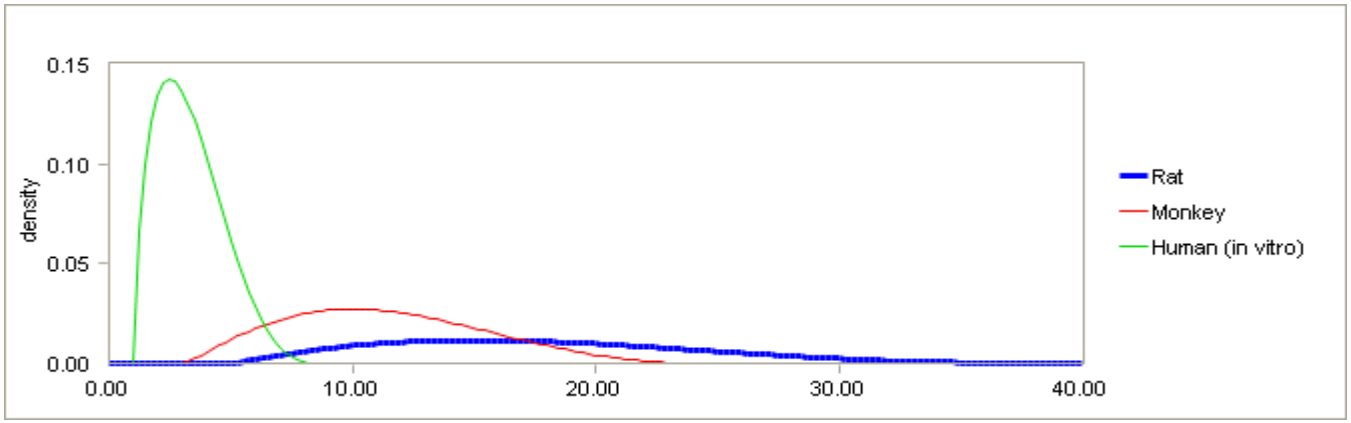
1. E.g. literature, expert opinion, clinical data;

2. Example:
   - What should be the dose for a first in human study;
   - Data available includes:
     - In vitro study
     - Animal data (e.g. rat, monkey)
   - What parameters to use?

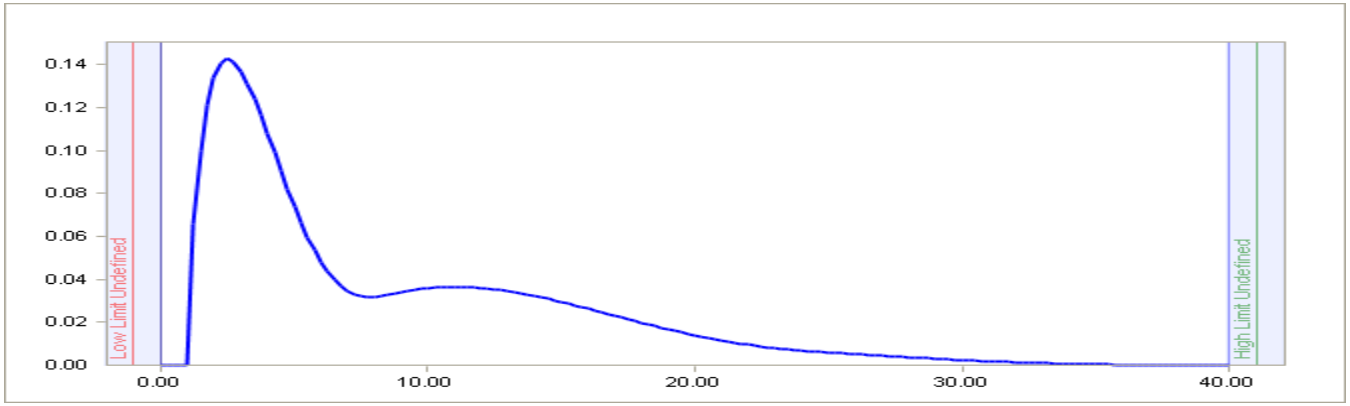
Note: This is not the same as a meta-analysis

Benefit 1.

With QRA, can take into account *different sources* of information and '*weight*' them for relevance;



Combined distribution (e.g. IC50):



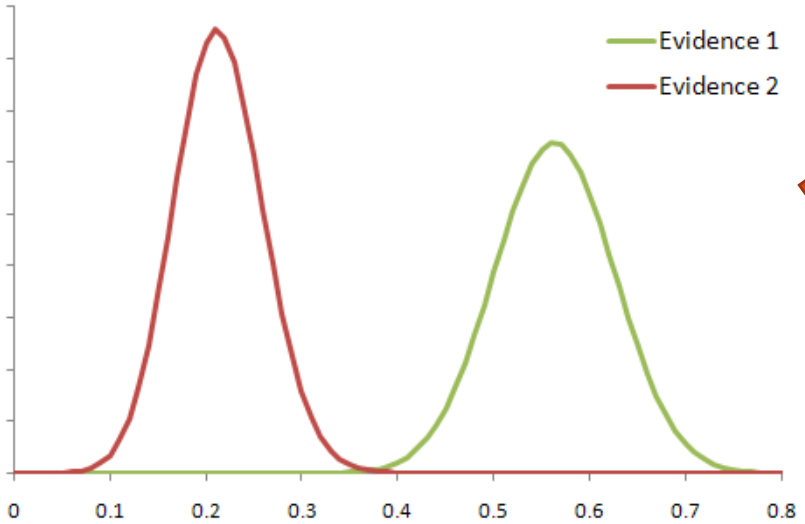
Benefit 1.

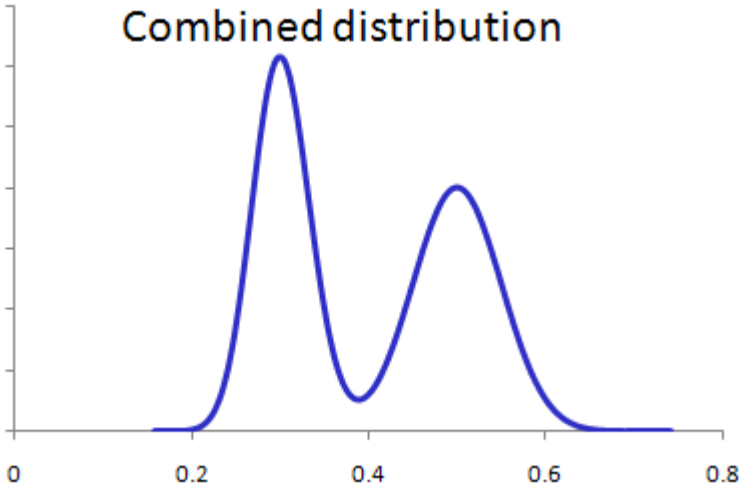
How does combining different opinions or sources of info differ from Meta-Analysis?

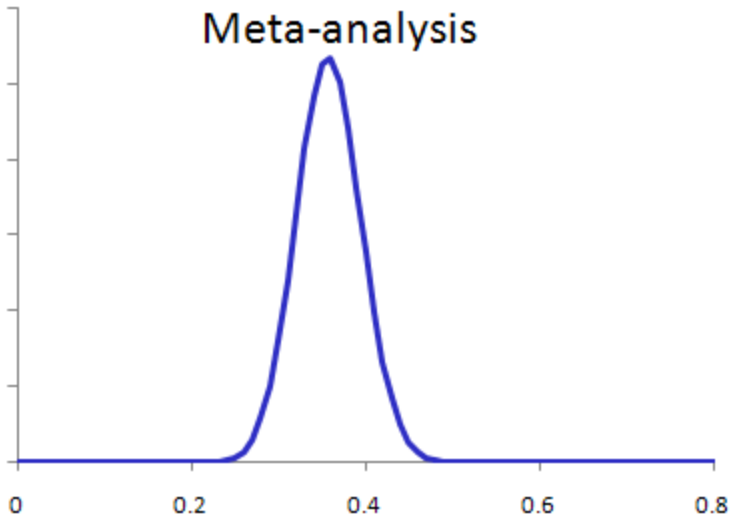
1. *Combining* **diverging** opinions or sources of information assumes that all sources are relevant but may not provide evidence about the same parameter or model. Sources are *subjectively weighted* by their credibility.

1. *Meta-analysis* assumes that all sources provide evidence for the *same parameter*, and they are weighted by the strength of their evidence using statistical methods (e.g. inverse variance). Thus, makes more assumptions.

Example – two sources of evidence for a probability *p* parameter, two options:







Benefit 2. Take into account variability and uncertainty

1. Uncertainty (lack of knowledge):
   - Parameter Uncertainty
   - Model Uncertainty

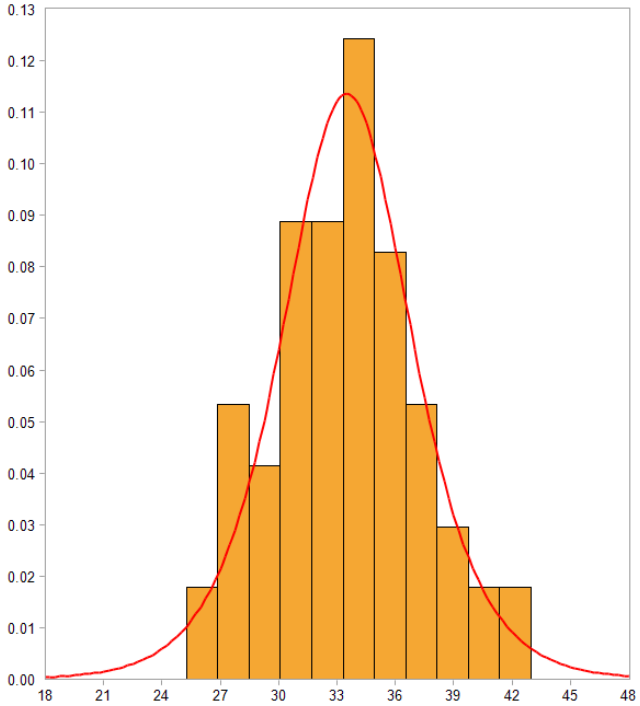
Especially relevant when there is little 'data'

1. Variability:
   - Patients within a clinical trial are randomly selected and will differ from patient to patient

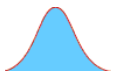
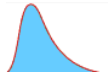
Benefit 2.

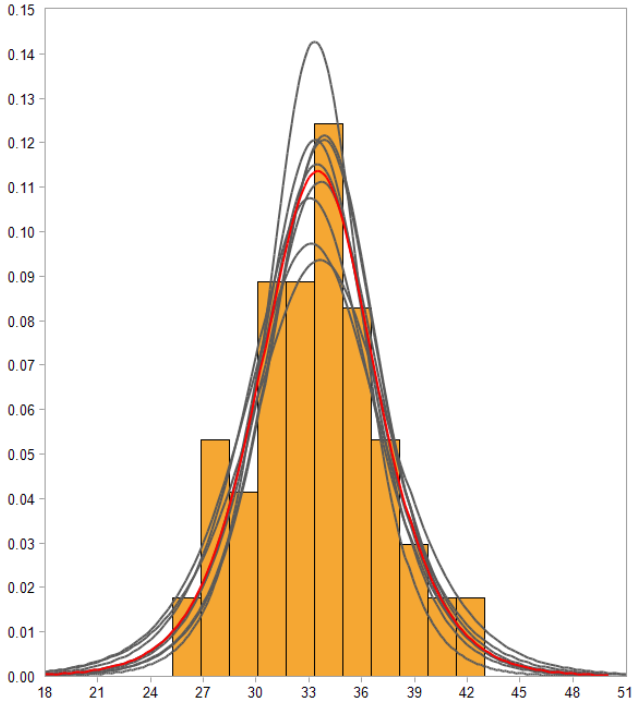
Variability only:

e.g. $N(\mu,\sigma)$



Variability and *parameter* uncertainty together:

$N($  ,  $)$



Benefit 2.

How to take into account *model* uncertainty?

- One way is Bayesian Model Averaging (BMA)
- Sometimes, we think 2 (or more) candidate models (e.g. distribution or regression) are plausible and relevant and we want to be able to use both…enter **Bayesian Model Averaging**
- Based on the idea that the better a model fits to relevant data, the more likely it is the 'right' model

Benefit 2.

So, how does BMA work…?

Can weight ('averaging') different models (e.g. distributions or regressions) according to the likelihood function

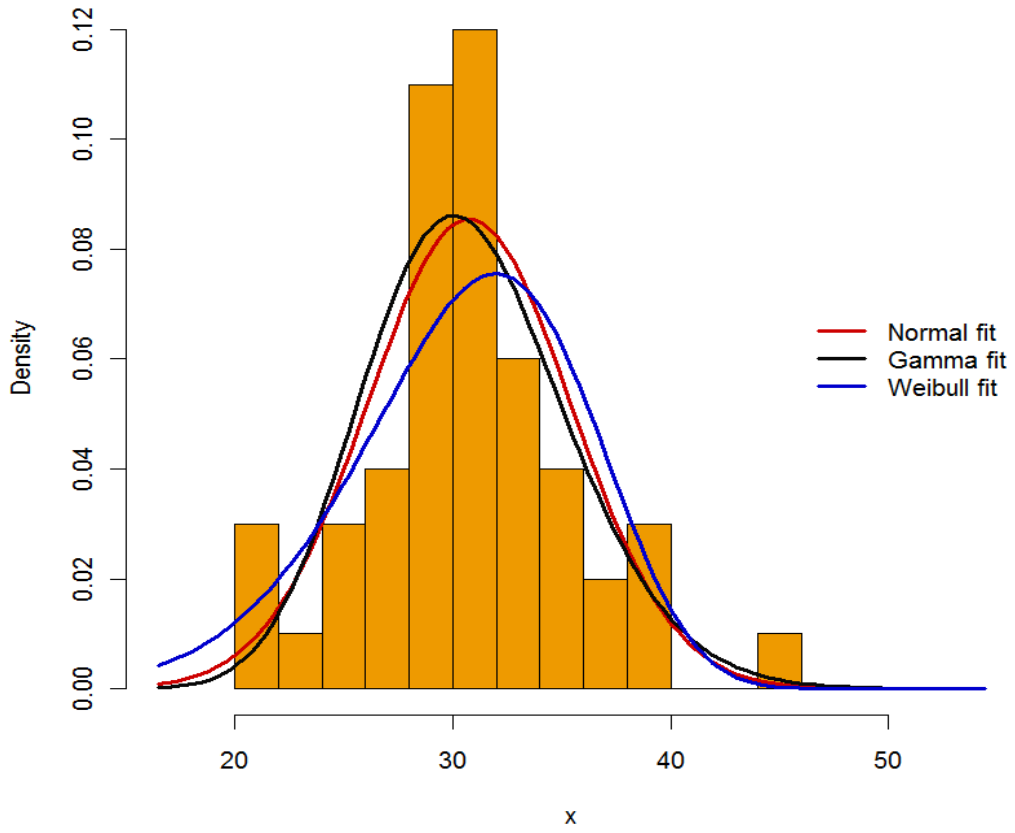
$$L(X \mid \alpha) = \prod_i f(x_i, \alpha)$$

BMA allow us to fit several plausible probability models to data using Bayes' Theorem

The method assumes Beta(1,1) priors, but can easily be used to assign prior weights (for example, based on frequency of usage of certain distribution in the literature)

Benefit 2.

So, how does BMA work…?



Benefit 3. Changes the questions decision-makers can ask, forces to think in 'ranges' and probabilities

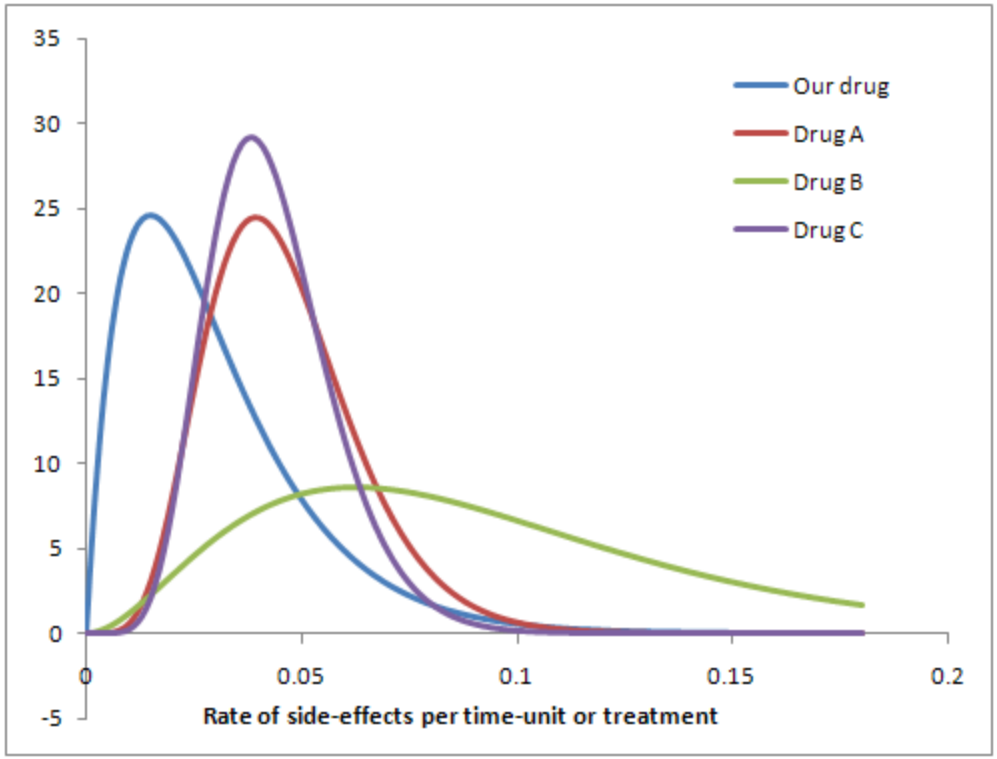
Example: Does our drug have less side effects than the competitor

Answer: Given the data, we can not reject the null-hypothesis of no difference (at p = 0.05, two sided test) between the rate of side-effects

Benefit 3.

Different question:

What is our confidence our drug has fewer side effects than drug A, B and C?



	Confidence
Drug A	76.1%
Drug B	91.3%
Drug C	77.3%

Benefit 4.

Fast, efficient and easy to access

- Typically performed within Excel with Monte Carlo Add-ins;
- Models and inputs can be used iteratively within a team-setting;
- Concepts typically much more intuitive to understand than other statistical/analytical methods

Summary:

1. QRA allows teams to combine wide range of data sources into one decision-supporting model;
2. Takes into account variability and uncertainty;
3. Reframes the team's questions;
4. Can be used iteratively and fast

Questions?

Dr. H.Groenendaal
Managing partner
EpiX Analytics LLC
Huybert@EpiXAnalytics.com
P: 303 440 8524