Equivalence of locally acting drugs based on pharmacodynamic data: a 1-step Dose-Scale method and use of trial simulations to assess sources of variability and power definitive studies

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OBJECTIVE

FDA and EMA have proposed using pharmacodynamic (PD) data to assess bioequivalence (BE) of locally-acting product. Dose-scale modeling (DSM) of PD data using a 2-step approach has been proposed, where the reference product is modeled in a first step, and scaling of the test to reference product is performed in a second step. Power calculations of BE studies using DSM are challenging due to the complexity of using of 2-step approach for sample size calculation, and the lack of understanding of sources of variability responsible for the width of 90% confidence intervals (CI). Alternatively a 1-step DSM method was applied to assess BE of locally acting product and simulations were performed to investigate the effect of key variables on the power of these studies to conclude BE.

METHODS

PD data were simulated based on real pulmonary data (methacholine provocation concentration producing a 20% fall in forced expiratory volume in one second PC20) and used to investigate the methodology of DSM to assess BE. The study had a 5-way cross-over, ten sequence William design with a placebo, two reference (REF) doses (90 and 180 mg) and two test (TEST) doses (90 and 180 mg).

The recommended FDA DSM methodology is to fit a REF dose-response model based on the placebo and REF data to estimate the relative potency (denoted by FREL) of the test compound. This approach can be done in two steps where the reference model is fitted first (on pooled REF data or mean reference data) then FREL is determined by fitting the TEST data fixing the parameters obtained from the REF model. The bootstrap Bca 90% CI are then obtained using the subject as a re-sampling unit. Alternatively FREL can be obtained by simultaneously fitting the TEST and REF data (1-step DSM) which is expected to provide equivalent results but with the advantage of being more efficient since it involves fitting one model and the bootstrap of the simultaneous model is easier to implement.

To illustrate the methodology, a DSM Emax model of log PC20 data with an additive residual error was used for simulation and the parameters used for the investigated scenarios are detailed in the Table below.

Variables	Typical value	BSV CV %
Baseline (E0)	0.9	20
Emax	3.5	20
ED50	90	20
FREL	1.00/0.95/1.05	10/20/50
Residual SD	0.2/0/0.4	
Sample Size (N)	90(5x18)	
Doses	(0,90,180)	
N bootstraps	100/1000	

A 1-step approach was used for simultaneously fitting the test and reference product using non-linear least square modeling and by constructing the bootstrap Bca 90% CI using sufficient bootstrap samples that produced stable CI's. Sufficient number of simulation replicates were performed (minimum of 100) to compute POWER and to identify the most important factors (e.g., residual error, between subject variability on parameters, FREL of TEST/ REF values) responsible for the width of 90% CI and for meeting the BE criteria (Bca limits of FREL between 0.8 and 1.25). The effect of total number of subjects was also investigated. The software used were S-plus (8.2, Tibco) and the resample library as well as R 2.15.0.

```
#S-plus code example to fit a 1-step dose-scale model and #obtain bootstrap
bca #intervals
############################################################
fit.nls <-  try(
nls(DV~ E0 +(DOSE*ifelse(FORM=="REF",1,exp(LFREL))*EMAX )
/(ED50+(DOSE*ifelse(FORM=="REF",1,exp(LFREL)))) , data=SIMDATA,
start=list(ED50=75,EMAX=log(1.5),E0=log(0.03),LFREL=0.010)
  )
                )
try.expr <- Quote({result <- try(coef(eval(fit.nls$call)))
                if(is(result, "Error")) rep(NA, 4) else result})
exp(coef(fit.nls)[4]) #  Frel value
summary(fit.nls ) # provides details on original data fit
############################################################
BOOTNLSMODEL <- bootstrap(SIMDATA, subject=ID,
try.expr,B=100,sampler=samp.bootstrap)
FRELBOOT<-
exp(mean(BOOTNLSMODEL100NOERR$replicates[,4],na.rm=T))
BCALIMITS<- exp(try(
limits.bca(BOOTNLSMODEL,probs=c( 0.05, 0.95))[4,]
                )   )
############################################################
```

RESULTS

The 1-step DSM method resulted in very similar 90% CI as compared to the 2-step DSM method and as such results for the 1-step method are reported hereafter. Depending on the variability of the parameters 100-2000 bootstrap replicates were necessary to obtain stable 90% CIs as assessed by graphical means.

Doubling the residual variability sd from the default value of 0.2 to 0.4 increased the width of the CI's by 66 % (from 0.09 to 0.15) as well as the point estimate of FREL (FIGURE 1A), however this had a minimal impact on the power to declare BE which was 95%.

Between-subject variability on FREL was varied from 10 to 50 %. Power was 100 % with BSV FREL = 10%, 95 % when BSV FREL = 20% and 75 % when BSV FREL = 50% (FIGURE 1B)

FIGURE 1A

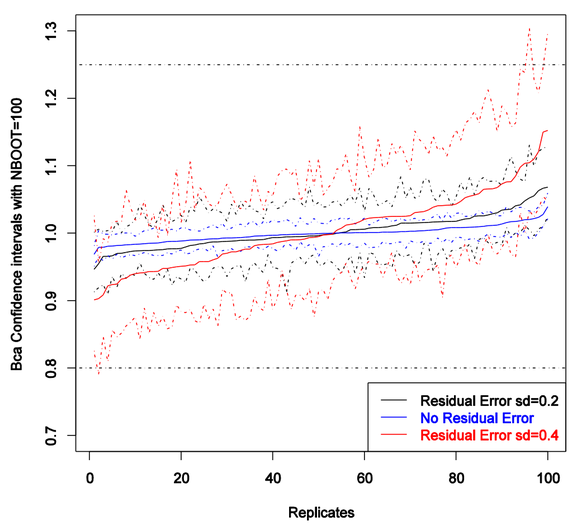
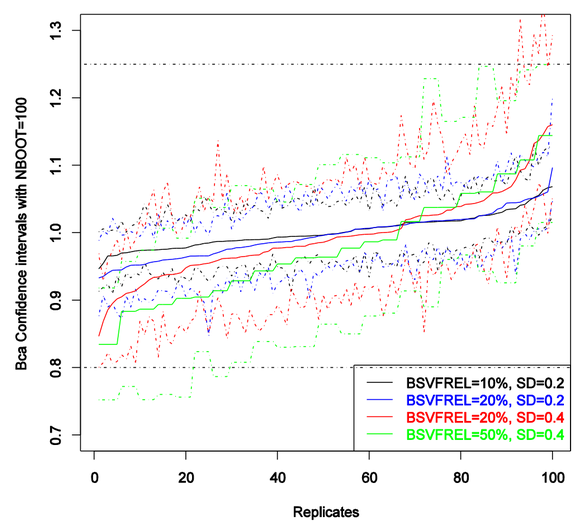


FIGURE 1B



When the point estimate of FREL was changed to 0.95 or 1.05 while fixing BSV FREL to 20 % or 50 % (FIGURE 2A) the point estimate of FREL were quite variable and the power to declare BE was: 92 % (BSV FREL 20 %, FREL=0.95), 90 % (BSV FREL 20 %, FREL=1.05), 75 % (BSV FREL 50 %, FREL=1.00), and 71 % (BSV FREL 50 %, FREL=1.05). Results were similar when number of bootstrap samples were increased to 1000, POWER = 73%. In addition, with 100 replicates, results were deemed stable as illustrated in (FIGURE 2B).

FIGURE 2A

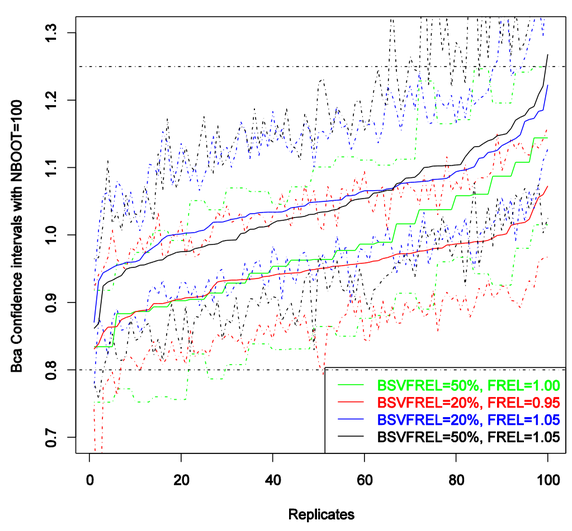
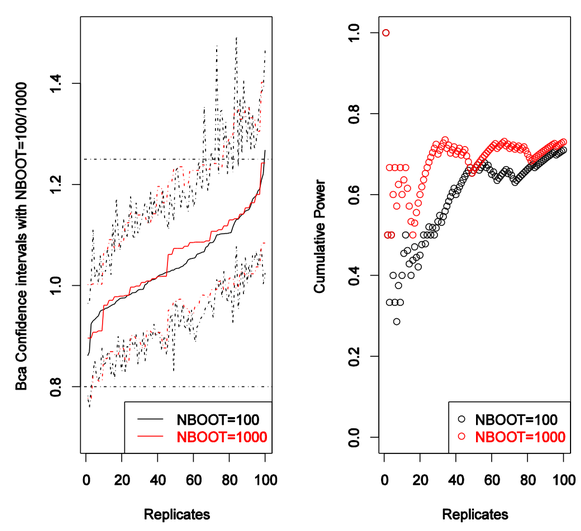


FIGURE 2B



The observed data that were available (data not shown) had an FREL BSV > 50 % and residual variability of about 20 %. As such we did not pursue scenarios with lower number of subjects since POWER with N=90 is already below 80 %.

The crucial part of the POWER determination were the between subject variability of FREL and the residual error. Using a pooled nonlinear least-squares fit might not be optimal since this method cannot separate the various levels of variability (Between-subject, Between-occasion, Residual). It is worthwhile to investigate individual mixed effect BE in these settings.

One possibility to increase the power is to only accept patients that provide a narrow reproducibility at the various visits: low residual error (better measurement methods for PD evaluations) and or low between-occasion variability (accept a given percent of variability for the visit specific baseline response).

CONCLUSIONS

The 1-step DSM method was used in order to investigated key variables responsible for optimally assessing the power of PD BE studies. Assuming a priori knowledge of dose-response curve, FREL point estimate and between-subject variability, trial simulations should be considered as the method of choice to power BE studies of pulmonary products (e.g., albuterol, glycopyrrolate) or locally acting gastrointestinal products (e.g., orlistat, misoprostol, mesalamine).