Statistical guidelines in Europe and USA – some conflicting issues)

Joint European Statistics Meeting

Paris 18-19 November 2010

Round Table

The Future of the European Statistical Guidance

Bernhard Huitfeldt

BH Statistical Consulting

FDA Guidelines - draft

- Non-inferiority clinical trials
- Adapative Design Clinical Trials
- Misssing data – NRC on behalf of FDA

http://www.fda.gov/opacom/morechoices/industry/guidedc.htm

Non-inferiority trials

Issue	FDA draft 2010	EMA - 2006
Synthesis method (T-P)=(R-P)+(T-R) or T/P=R/P * T/R	Only for relative efficacy (T vs R)	OK for absolute efficacy (T vs P) if a conservative margin is defined
50 % of (R-P) efficacy should be retained	Standard approach	”Not appropriate” ”Not acceptable”
Clinically meaning-ful effect in relation to defining NI-margin	Lower end of confidence interval	Point estimate

Adaptive designs

Issue	FDA –draft 2010	EMA 2007
General impression – the ”tone”	Relatively positive	Relatively negative
Scope of guidance	Broad	Narrow
Major advice	Pre-planning Type 1 control Blinded if possible	Pre-planning Type 1 control Blinded if possible

Missing data

Issue	National Research Council on behalf of FDA (2010) - draft	EMA – 2001 (rev 2008)
Single imputation (LOCF)	Still standard within FDA, but considered mostly inadequate in draft report	Only appropriate under certain restrictive assumptions
Use of likelyhood based methods, e.g. MMRM	Encouraged	Encouraged