



# The MCP-Mod methodology and beyond

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EFSPi Meeting - Dose Selection in Late Phase Clinical Development

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# Outline

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- MCP-Mod (**M**ultiple **C**omparison **P**rocedure – **M**odelling)
  - Background
  - Simulation based comparison: MCP-Mod vs ANOVA
  - EMA qualification opinion on MCP-Mod
- Messages from EMA/EFPIA dose-finding workshop
- Beyond cross-sectional dose-response modelling
- Beyond dose-finding in Phase II

# What is MCP-Mod?

## *Multiple Comparison Procedures – Modelling: Overview*

- A method for model-based dose-response testing and estimation
  - MCP-step
    - Establish a dose-response signal (the dose-response curve is not flat) using multiple comparison procedures
  - Mod-step
    - Estimate the dose-response curve and target doses of interest ( $ED_{50}$ ,  $ED_{90}$ , MED, etc) using modelling techniques
- What is special about the approach (for a modelling approach)?
  - Modelling **pre-specified** at design stage as primary analysis
    - Design (doses & sample size) tailored to the needs of the analysis method
  - **Model uncertainty** at design stage is addressed by using
    - a candidate set of models (for MCP and Mod step)
    - & a procedure on how to perform model selection (or model averaging)

# What is MCP-Mod?

## *Multiple Comparison Procedures – Modelling: At Novartis*

- Method developed Novartis internally in ~ 2004
- Since then used in > 15 completed studies with df element
  - often as primary analysis

Drug	Phase	Condition studied	Treatment groups
1	Phase IIb	Gout	5 doses, AC
2	Phase IIb	Diabetes	PBO, 4 doses
3	Phase III	Prevention of cardiovascular events	PBO, 3 doses
4	Phase IIb	Psoriasis	PBO, 3 od and 4 bid doses
5	Phase IIb	Multiple Sclerosis	PBO, 5 doses
6	Phase IIa/b	Epilepsy	PBO, 2 doses
7	Phase II	Hypertension	PBO, 3 od doses, 1 bid dose
8	Phase IIb	Diabetes	PBO, 5 doses, AC
9	Phase III	Familial Chylomicronemia Syndrome	PBO, 2 doses
10	Phase II	Hypertriglyceridemia	PBO, 3 doses, 2 AC
11	Phase IIb	Hypertension	PBO, 3 doses, 3 AC
12	Phase IIb	Diabetes	PBO, 7 doses
13	Phase IIb	COPD	PBO, 4 od doses, AC
14	Phase IIb	COPD	PBO, 3 bid doses, 4 od doses
15	Phase IIb	Asthma	PBO, 9 od doses, 4 bid doses, AC
16	Phase II	COPD	PBO, 4 doses
17	Phase IIa	Dental pain	PBO, 6 doses, AC
18	Phase II	Generalized anxiety disorder	PBO, 4 doses

# MCP-Mod: Dose-response modelling under model uncertainty

see **Bretz et al (2005)**, *Biometrics* & **Pinheiro et al (2014)**, *Statistics in Medicine*

## Trial Design Stage

### General design considerations

Determination of suitable study population, endpoints, etc.

### Set of candidate models

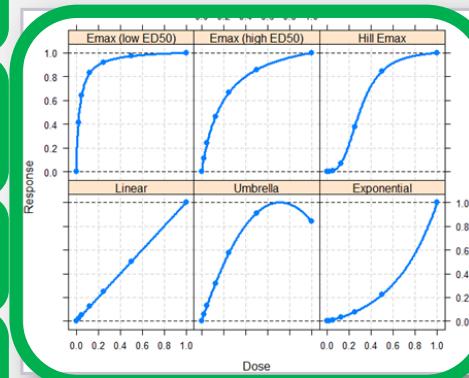
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

### Optimal statistical tests

Optimized for candidate dose-response shapes

### Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



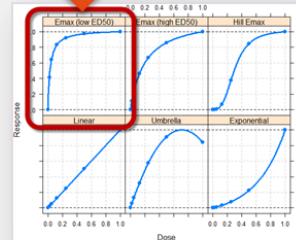
Trial conduct

## Trial Analysis Stage

### MCP step

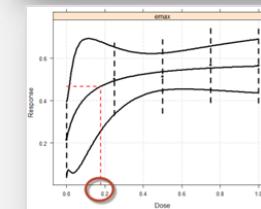
- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models

$p < \alpha?$



### Mod step

Dose-response and target dose estimation based on selected model(s)



# MCP-Mod: Implementations

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- DoseFinding R package
  - [\*https://cran.r-project.org/package=DoseFinding\*](https://cran.r-project.org/package=DoseFinding)
  - Design and analysis
- ADDPLAN-DF (ICON)
  - Extensive design & simulation features
- EAST, PROC MCPMOD (Cytel)
  - EAST – Design aspects
  - PROC MCPMOD – Analysis (SAS extension)

# Scope of MCP-Mod

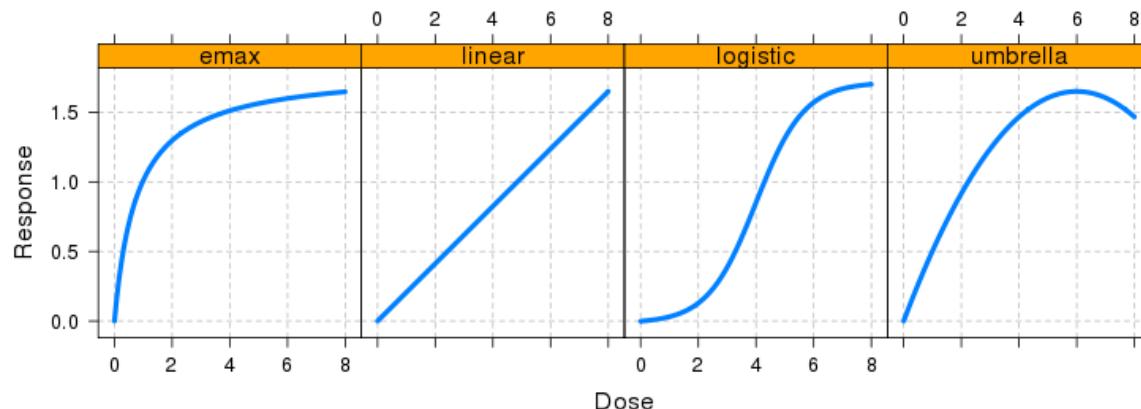
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- Development Phase
  - Ph II dose-response studies to support dose selection for Phase III
- Response can be continuous, binary, count, time-to-event
- Number of doses, dose-range
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendations (rules of thumb): 4-7 active doses, >10-fold dose range
- Control
  - MCP-step makes most sense when there is a placebo control in the trial
- Primarily used for cross-sectional dose-response analyses and when interest is in one regimen
  - But some of the ideas could be extended to other applications: cross-sectional exposure-response, longitudinal, different regimen

# Simulation comparison to different ANOVA designs

Simulation scenarios as in: *J. Biopharm. Statistics* (2007), 17, 965-995.

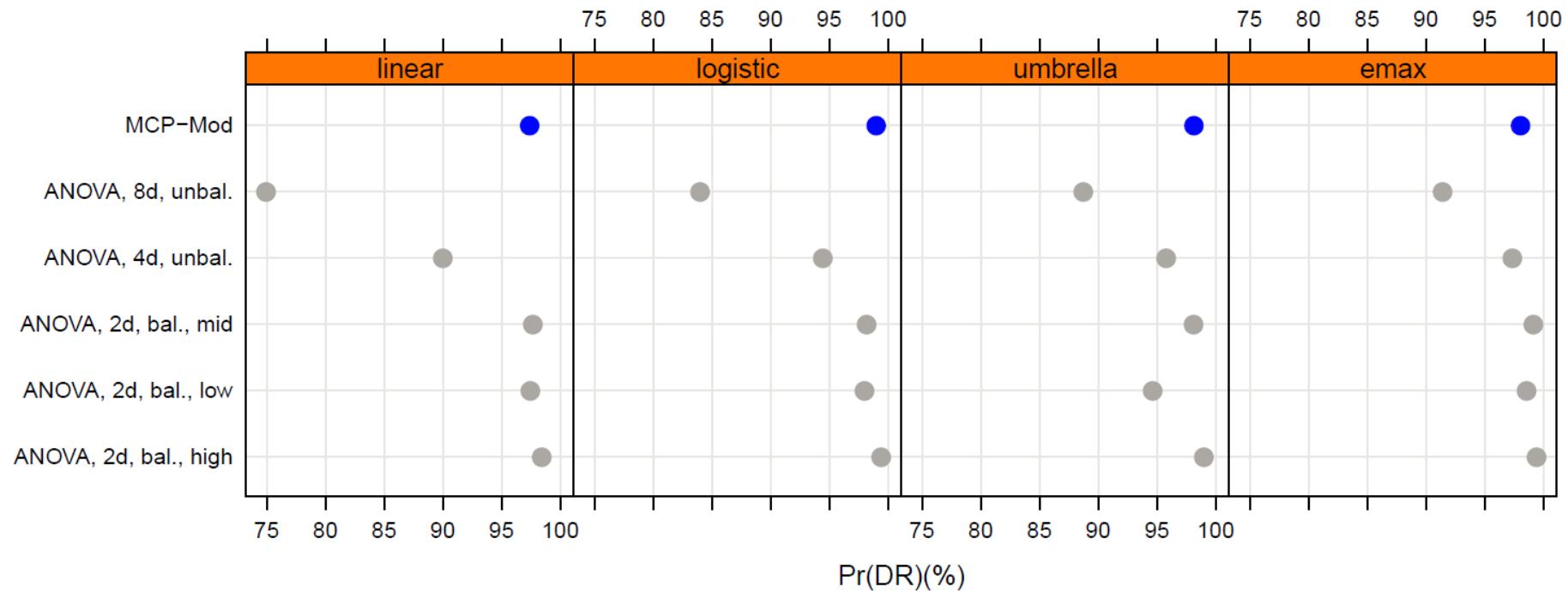
## Scenarios for mean (sample size, $\sigma^2$ realistic)



- MCP-Mod, optimal unbalanced design (PBO & 4 active doses)
  - 0, 0.54, 3.2, 4.8, 8 (D-optimal design), 1.5:1:1:1:1.5
- ANOVA optimal unbalanced design on 4 & 8 doses & PBO
  - Allocation according to square-root rule (more patients on PBO)
- ANOVA balanced allocation 2 doses & PBO
  - PBO & 2 active doses, vary the low dose (low (2), mid (4), high (6))

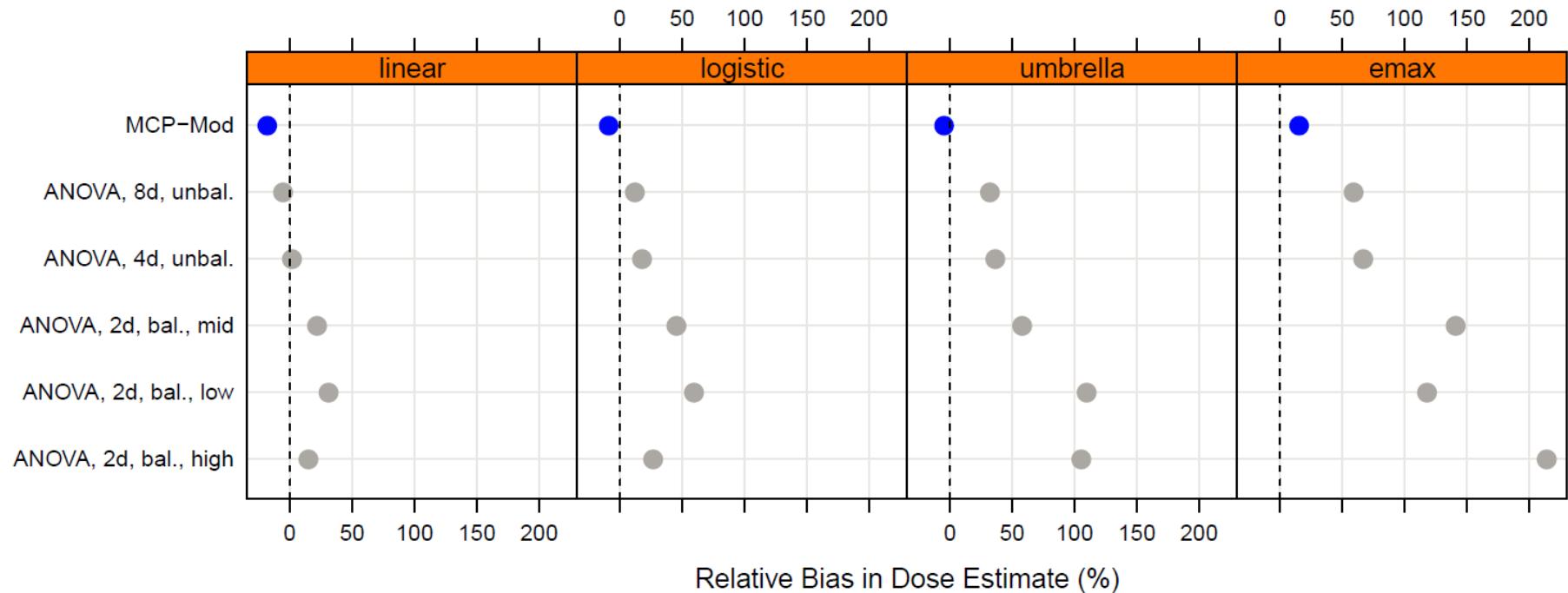
# Simulation comparison to different ANOVA designs

*Power to detect dose-response trend (larger is better)*



# Simulation comparison to different ANOVA designs

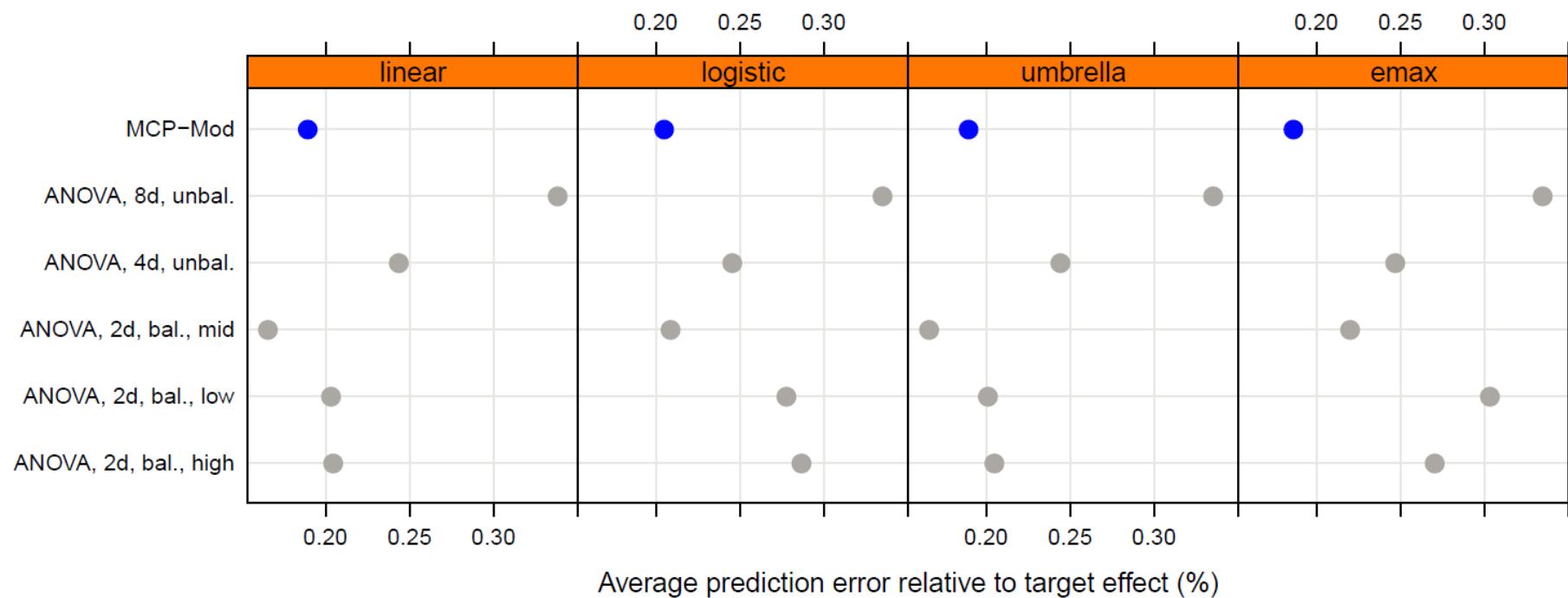
*Bias in target dose\* estimate (closer to zero is better)*



\*Target dose: Smallest dose achieving a clinically relevant effect of 1.3 over placebo

# Simulation comparison to different ANOVA designs

*Estimation error for dose means (smaller is better)*



# Simulation comparison to different ANOVA designs

## Conclusions

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- Dose-response modelling typically as good as the best of 5 ANOVA approaches
  - no single ANOVA approach similarly robust
  - Examples:
    - ANOVA 8d performs well for estimating the target dose, but worse in terms of power and dose-response estimation
    - ANOVA 2d high performs well if the true dose-response is linear, but very bad if the true dose response is of Emax type
- Performance of ANOVA is sensitive to underlying shape
  - in particular if the number of doses is small
  - if the number of doses (within an ANOVA approach) is larger the power detoriates

# CHMP Qualification Opinion

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- The European Medicines Agency (via the CHMP) offers scientific advice to support the qualification of **innovative development methods** for a **specific intended use** in the context of research and development into pharmaceuticals.
  - Examples: **novel methodology, imaging method or biomarker.**
- First opinion issued in 2010, since then 12 qualification opinions (biomarkers, technologies/devices, simulation models)
  - MCP-Mod **first statistical methodology** qualified

# CHMP Qualification Opinion



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 January 2014  
EMA/CHMP/SAWP/757052/2013  
Committee for Medicinal Products for Human Use (CHMP)

## Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013 <sup>1</sup>
Start of public consultation	15 October 2013 <sup>2</sup>
End of consultation (deadline for comments)	24 November 2013 <sup>3</sup>
Adoption by CHMP	23 January 2014

# Quotes from qualification opinion

## Summary

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- “... *The MCP-Mod approach is efficient in the sense that it uses the available data better than the commonly applied pairwise comparisons...*”
- “... *the methodological approach will promote better trial designs incorporating a wider dose range and increased number of dose levels...*”
- “... *Properly implemented however, the benefits include not only efficient data collection and more precise answers to important questions [...] but should also serve to enhance discussions with stakeholders in advance of the trial comparing different strategies and explaining risks and limitations of potential designs. ...*”

# Quotes from qualification opinion

## Other Modelling Approaches

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- “*... It is fully appreciated that certain benefits that may be derived from an MCP-Mod approach would also be derived from other model-based approaches and that modelling approaches are not restricted to those based on dose-response. MCP-Mod represents one tool in the toolbox of the well-informed drug developer. In that sense, this opinion does not preclude any other statistical methodology for model-based design and analysis of exploratory dose finding studies from being used....*”

# Quotes from qualification opinion

## On type I error control in Phase II

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- “*...Designing an experiment that permits conclusions to be drawn with control of false-positive error rate is clearly desirable for the study sponsor. It is mandated by regulators in the confirmatory phase of development, though not in the exploratory phase that is under discussion here, where factors other than strict type I error control may influence decisions regarding future clinical development. The choice of 5% used by the Applicant in their illustrations is arbitrary and could be varied based on the certainty that the Applicant wish to have for their decision-making...*”

# Quotes from qualification opinion

## Other messages

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- “... many of the ‘best-practice’ approaches described by the authors, for example the inclusion of multiple dose levels and attempting to quantify dose-response curves are explicit in this regulatory document [ICH E4 guidance on dose-response] and despite **not being widely practiced**, are **welcomed** and regarded as **uncontroversial...**”
- “...it is arguable therefore that to qualify MCP-Mod as an improvement over the commonly used approach is **uncontroversial from a regulatory perspective**. [...] yet the use of this type of approach in regulatory submissions remains rare and hence, **the fact that these sub-optimal approaches persist makes this a relevant topic for a CHMP opinion...**”

# Comments

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- Positive CHMP qualification opinion on MCP-Mod
  - Emphasizes importance of well designed dose-finding studies
  - Illustrates openness towards model-based approaches
    - one among a few ongoing EMA initiatives in this direction
      - concept paper on extrapolation
      - EFPIA/EMA workshops on dose-finding (2011, 2014)

# EMA/EFPIA workshop on dose-finding

December 2014



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

Agenda - EMA EFPIA Workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products

04 – 05 December 2014, meeting room 3A  
30 Churchill Place, Canary Wharf, London E14 5EU

- Attended by industry, regulatory, academia
  - modellers, statisticians, clinical pharmacologists, clinicians
  - senior regulators in Europe (e.g. chair of CHMP, chair of SAWP, heads of national regulatory agencies in Europe)
    - FDA Pharmacometrics & FDA Biostatistics group, PMDA
  - Industry representatives
- Fully available on YouTube

[https://www.youtube.com/playlist?list=PL7K5dNgKnawYdGxvT1aGPI9v2wMf\\_QkTj](https://www.youtube.com/playlist?list=PL7K5dNgKnawYdGxvT1aGPI9v2wMf_QkTj)

# EMA/EFPIA workshop on dose-finding

December 2014

Regulatory experience, both FDA and EMA, shows that phase 2 is often abbreviated and simplified in order to move as quickly as possible to pivotal trials (and also the hope to have the simplified phase 2 study serve as one of the pivotal studies), the selection of dose is frequently empirical and rarely scientifically sound, and the D-E-R is poorly characterised due to the limited dose range tested in phase 2.

The reasons for reduced standards in phase 2 lies in the fact that drug development is costly/competitive and accelerated access to the market is a considerable incentive for sponsors. Although it is acknowledged that in some cases the need to provide rapid access to the patient outweighs the need to optimise the dose (i.e. breakthrough treatments for cancer), regulators and industry alike agree that this strategy at large could prove very risky and is short sighted. Poor dose selection will in turn often lead to failed phase 3 trials, delayed/denials of regulatory submissions and/or changes in doses post-approval (Sacks et al, JAMA. 2014;311:378-384, Cross et al Pharmacoepidemiology and Drug Safety 2002; 11: 439-446), additional post-marketing commitments

Regulators clearly identify dose selection as a "shared risk". In the past dose selection was erroneously referred to as "the sponsor's risk". The notion was reinforced by the fact that scientifically rigorous and optimal dose selection is not a requirement by US or EU law. Nevertheless, the wording is unfortunate and should be taken to mean that a sub-standard approach to dose finding and understanding D-E-R represents a risk to the development programme.

Workshop report:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2015/04/WC500185864.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf)

# EMA/EFPIA workshop on dose-finding

December 2014

**Table 1 Key learnings**

Dose selection is a **shared risk**

**D-E-R characterisation** is a key component of the development and evaluation of medicinal products. Especially for children, elderly and ethnic groups this is the mainstay of drug development. Failure to reproduce this information at the stage of MAA, misses the opportunity to mitigate regulatory uncertainties and may result in denial, delays in approval, and additional regulatory requirements in terms of post approval commitments

Traditional statistical **pairwise comparisons** in phase 2 trials to support dose selection, by testing for statistically significant differences between the groups **are not a regulatory requirement, and are suboptimal** in terms of dose selection

**Dose ranging studies** should be designed for estimating dose response characteristics. As many as 4-7 active doses across a >10-fold range (e.g. 0.1 - 1.0 of the maximum tolerated dose-MTD) might be targeted **adapting to the reality** of the specific drug and disease state

Mathematical, statistical and pharmacological **methodologies** to characterise D-E-R and optimal dose selection are scientifically well developed, available for application and welcomed by regulators. These should be tailored to the specific development needs

Workshop report:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2015/04/WC500185864.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf)

# EMA/EFPIA workshop on dose-finding

December 2014

## Table 2 Next Steps

Establish a post-workshop expert group with representation from regulatory bodies, industry and academia to progress areas of discussions and actions identified. This group will work towards emphasising the importance and promoting good practices for dose selection and D-E-R characterisation. Two publications, one addressing methodologists and one addressing late phase decision makers, will be the first outcomes of this group.

In addition it is envisaged that discussions will continue at product level, i.e. scientific advice, PIP submissions, at MAA, or methodology level, i.e. qualification procedures.

Update of the **CHMP assessment report templates** to reinforce the importance and facilitate the evaluation of dose-exposure-response relationships at the stage of MAA, to support B/R decisions and to inform the Risk Management Plan (RMP).

Debate the need to create/update a **regulatory guidance** on dose finding.

### Follow

- Update on ICH E4 guidance on dose-response (?)  
20 years old, but perceived to not have had the desired impact
- New dose-finding guidance (?), update of FDA exposure-response guidance (?)

Workshop results  
<http://www.eudra.org>

# EMA/EFPIA workshop on dose-finding

December 2014

The slide is a template from the U.S. Food and Drug Administration (FDA). It features a blue header bar with the FDA logo, the text "U.S. Food and Drug Administration Protecting and Promoting Public Health", and the website "www.fda.gov". Below the header is a white main content area with a blue wavy footer bar containing the number "6".

## Summary

- Not sufficient to support the safety and efficacy of one dose relative to placebo/control
- Search for dosing regimen with optimal safety/efficacy profile or even individualized dose(s)
- Impact of dose-exposure-response information
  - Approval
  - PMC/PMR

Presentation by Yaning Wang, (FDA, Pharmacometrics): “Impact of D-E-R Information on Regulatory Approval and Post Authorisation Commitments”

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2015/01/WC500179818.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/01/WC500179818.pdf)

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# **Beyond cross-sectional dose-response modelling**

# Beyond cross-sectional dose-response

*Challenges for cross-sectional dose-response approach*

- Different treatment frequencies or regimen for loading & maintenance
  - In special situations possible to model the dose-response curves (at steady state) in the regimen, when there are enough doses
    - Borrowing of strength possible by assuming some parameters are shared  
Example: For regimen r use
- Drugs with long half-life and no steady state of effect
  - What is „the dose-response“?
    - Time-point for dose-selection?
  - If dosing is not daily, dosing frequency is as important as „dose“ itself

# Beyond cross-sectional dose-response

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## ■ Longitudinal dose-response modelling

- Model dose-response relationship over time
  - E.g. use (see Tan et al. 2011)

$$f(d, t) = E_0(t) + E_{\max}(t) \frac{d}{ED_{50}(t) + d}$$

and parametric models for  $E_0(t)$ ,  $E_{\max}(t)$  and  $ED_{50}(t)$ .

- Advantages:
  - Borrowing of strength between time-points
- Challenges
  - Different treatment frequencies or regimen for loading & maintenance
  - Which parametric form for development over time?

# Beyond cross-sectional dose-response

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- Cross-sectional / steady state dose-exposure-response modelling
  - Instead of dose, use exposure (measured or estimated) as input to a exposure response analysis
  - Advantages
    - Part of the variability in response might be due to variability in drug exposure (more efficiency in estimation)
    - More potential to integrate information between regimen or administration forms in one model
    - More scientific insight (more potential for extrapolation)
  - Challenges
    - Which exposure metric is adequate (is there any)? How to model delay between exposure and response?
    - „Breaks randomization“ if patients are not randomized to exposure levels
      - unobserved confounding factors might act on dose-exposure and exposure-response simultaneously (however: some diagnostics available to detect this)

# Beyond cross-sectional dose-response

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- Longitudinal dose-exposure-response modelling
  - Model dose-exposure and exposure-response over time (see e.g. Källén, 2008)
  - Advantages
    - Part of the variability in response might be due to variability in drug exposure (more efficiency in estimation)
    - Integration of information between regimen or administration forms in one model
    - Most scientific insight (most potential for extrapolation)
  - Challenges
    - How to model delay between exposure and response?
    - Most complex model to build

# Beyond cross-sectional dose-response

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- More complex models challenging to specify prospectively (at the current standards of pre-specification)
  - For post-hoc developed models
    - Issue of stability (how sensitive is the selected model & covariates to specifics of the data-set it has been developed upon), in particular for covariate selection
      - Some statistical tools as a partial solutions: model averaging, bagging, ...
  - Progress on model checks/validation & standards for model building

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# Beyond dose-finding in Phase II

# Dose-Finding in Drug Development

*Of course not only in Phase II*

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- Pre-clinical
  - Human dose extrapolation
- Phase I First in human trials
  - Safety dose-finding (MTD)
- Phase II
  - Efficacy dose-finding: Demonstrate that chosen dose is not excessive
- Phase III
  - Demonstration of benefit/risk

# More than one dose (dose-finding) in Phase III

## *Advantages*

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- Less dependence on extrapolations from Phase II
  - Long term safety, broader population & sometimes clinical efficacy not studied in Phase II
  - More complete information on benefit/risk
  - Better dose-finding
- More chances to select an adequate dose as two (or more doses) are used

# More than one dose (dose-finding) in Phase III

## *Disadvantages*

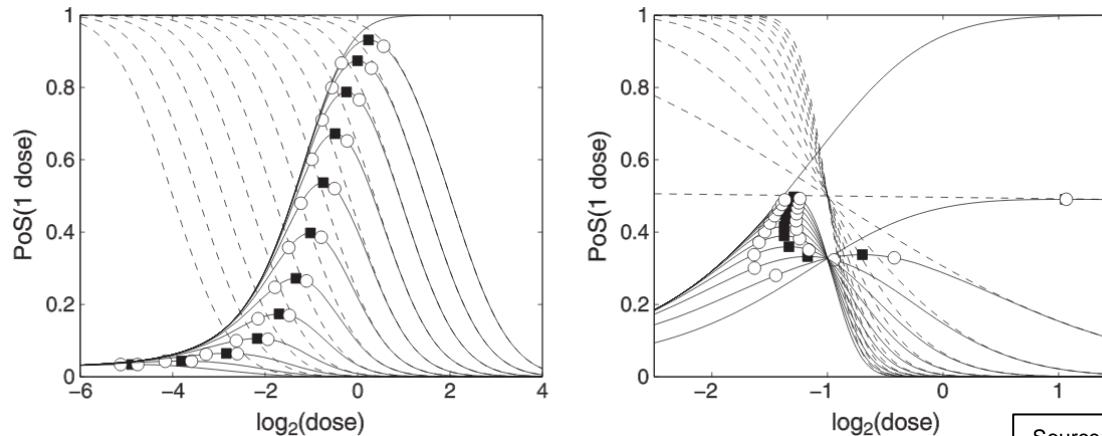
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- Usually a longer trial with more sample size
- Exploratory and confirmatory aspects in one trial
  - Aims can be conflicting
  - Challenge for design and planning of analysis (e.g. strict control of familywise error rate, as well as exploratory aspects etc)  
→ König (2015): Closed MCP-Mod procedure
- Potentially more discussion on the dose(s) to be used
  - Is this a disadvantage?

# More than one dose (dose-finding) in Phase III

Comparing two vs one dose in Phase III for same total sample size

- Lisovskaja & Burman (2013) investigate the problem systematically
  - Using the probability of success:  $p(x)q(x)$ 
    - $p(x)$ : Power of the trial (efficacy) at dose  $x$   
Depends on Emax function, sample size, standard deviation
    - $q(x)$ : Probability dose  $x$  regarded as tolerable by regulators  
Gaussian cdf in log dose (two parameters)



Source: Lisovskaja V. and Burman, C.F.  
(2013) Statistics in Medicine, 32, 1661–1676

# More than one dose (dose-finding) in Phase III

*Comparing two vs one dose in Phase III for same total sample size*

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- Using reparameterizations, the problem can be reduced to 3 parameters and thus systematically studied
- Major conclusions
  - Clear: For the same sample size per arm (i.e. larger total sample size for the two dose design), two-doses typically will outperform the design with one dose in terms of probability of success
  - Two-dose designs in a number of scenarios outperform one-dose designs (**for the same total sample size**), when there is uncertainty of the efficacy curve and/or uncertainty on the tolerability
  - When novel multiple testing strategies are being used the benefit is even increased

# References

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