Implementing a novel statistical methodology in pharmaceutical industry

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Summary

- MCP-Mod (Multiple Comparisons Procedures & Modeling)
  - an approach for statistical analysis of Phase II dose-finding studies using a combination of testing and nonlinear regression techniques

  2003
  - Developed within Novartis stat group to improve dose-finding methods

  2014
  - Method has been adopted in ~20 Novartis dose-finding studies and is used in most of the Novartis dose-finding studies (when appropriate)
  - Method is being used by other major pharmaceutical companies
  - Received a positive qualification opinion from EMA (European Medicines Agency), first time EMA has „qualified“ a statistical method

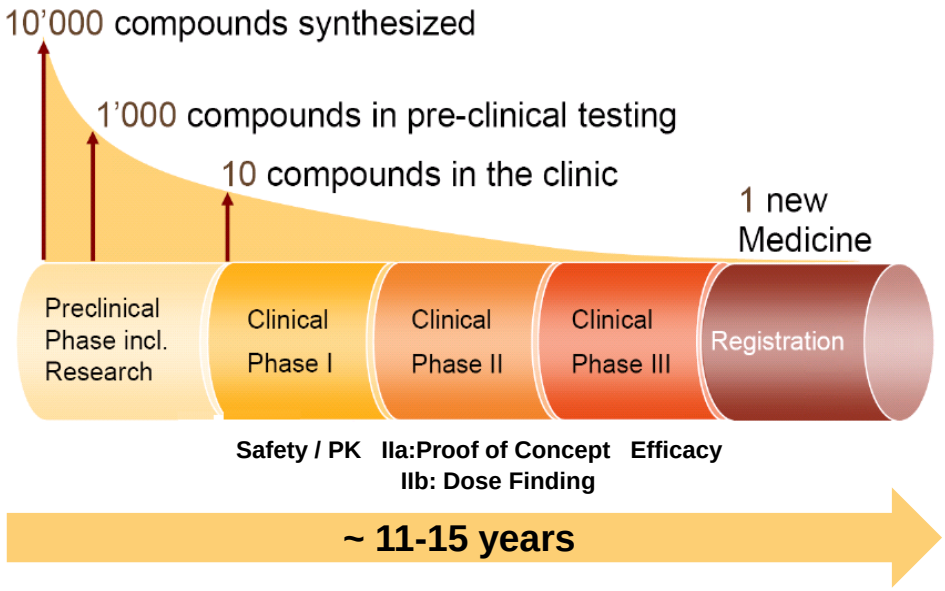
- This presentation is about what happened inbetween

Outline

- Pharmaceutical Industry
- MCP-Mod story
  - The starting point: Biostatistics dose-finding initiative
    - Objectives in Phase II dose-finding studies
  - Technical description of MCP-Mod methodology
  - How to get it implemented in clinical trials
    - Internal & External Focus
    - Technical Enabling
    - Other factors
  - Remarks

Pharmaceutical industry

A regulated environment



- After End of Phase III
  - Health authorities scientifically review quality, safety and efficacy of application & are the ones to grant marketing authorization of drugs
  - Innovation needs to convince not only decision makers within the company but also regulatory bodies

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Pharmaceutical industry

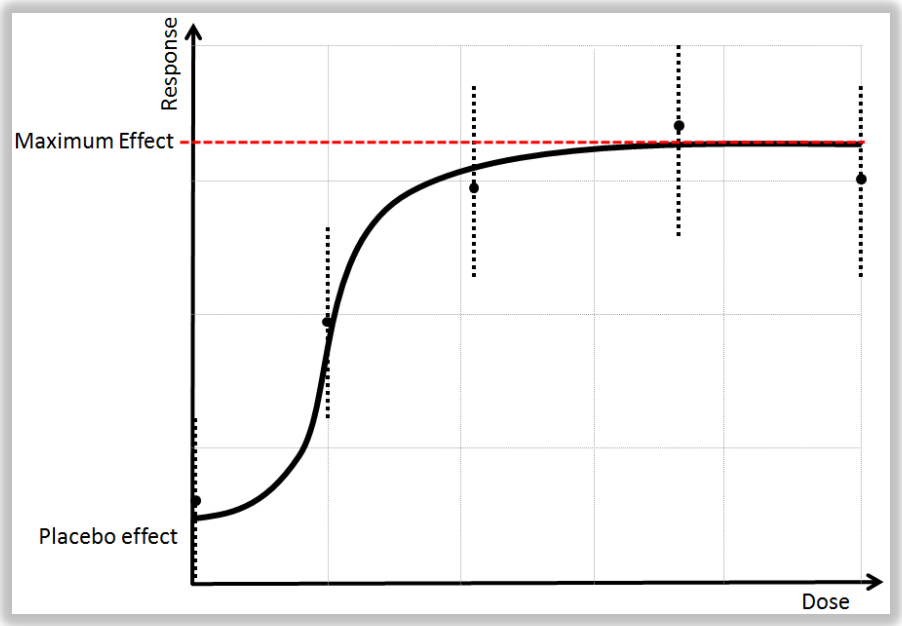
A regulated environment

- An immediate regulatory opinion on an innovative solution is often not available
  - if acceptability of an approach is questionable, using established approaches is the typical risk-averse strategy
  - situation leads to tendency towards conservatism (in the companies)
  - (regulators support innovation in different forms, e.g., offer scientific advice meetings)
- Other challenges for innovation (not specific to pharma)
  - Need to convince project team members and more senior decision makers with varied backgrounds of benefits of the new approach
  - Tendency towards standardization of work flows. Innovation changes existing standards and requires rethinking (and often more work at least initially)

Dose-Finding in Phase IIb

Objectives

- Determine the (efficacy) dose-response relationship
  - Is there a dose-related effect at all?
  - What is the maximum effect size?
  - What is the nature of the dose-response shape?
    - Where is the increasing part of the dose-response curve
    - Where does the dose-response start to plateau?
  - Safety/tolerability dose-response curve



- Ultimate aims
  - Be able to make go/no go decision to Phase III reliably
  - If we go
    - which dose(s) to choose (which doses have the best benefit-risk relationship)?

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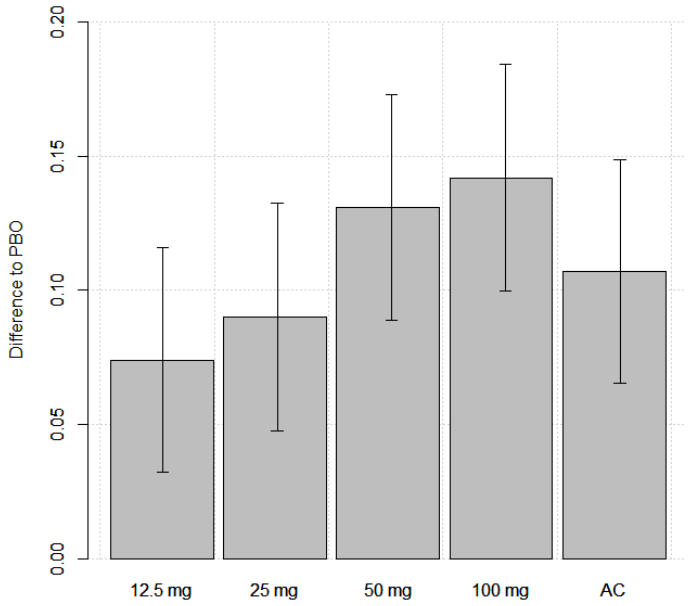
Motivation to improve Phase II dose-finding

Start of informal dose-finding initiative (~2002)

- Mis-match between real objectives and objectives in protocol
  - Statistical objectives in protocol
    - testing hypotheses: control versus active doses
    - Study design determined by this objective (sample size, number of doses, dosages used (typically kept at minimum), ...)
  - Output of a pairwise analysis



- Conclusion
  - All active doses (& the active comparator (AC)) are significantly different from placebo
- What happens in-between observed doses/what is the dose-response curve?
- Which doses gives equivalent efficacy as the AC?

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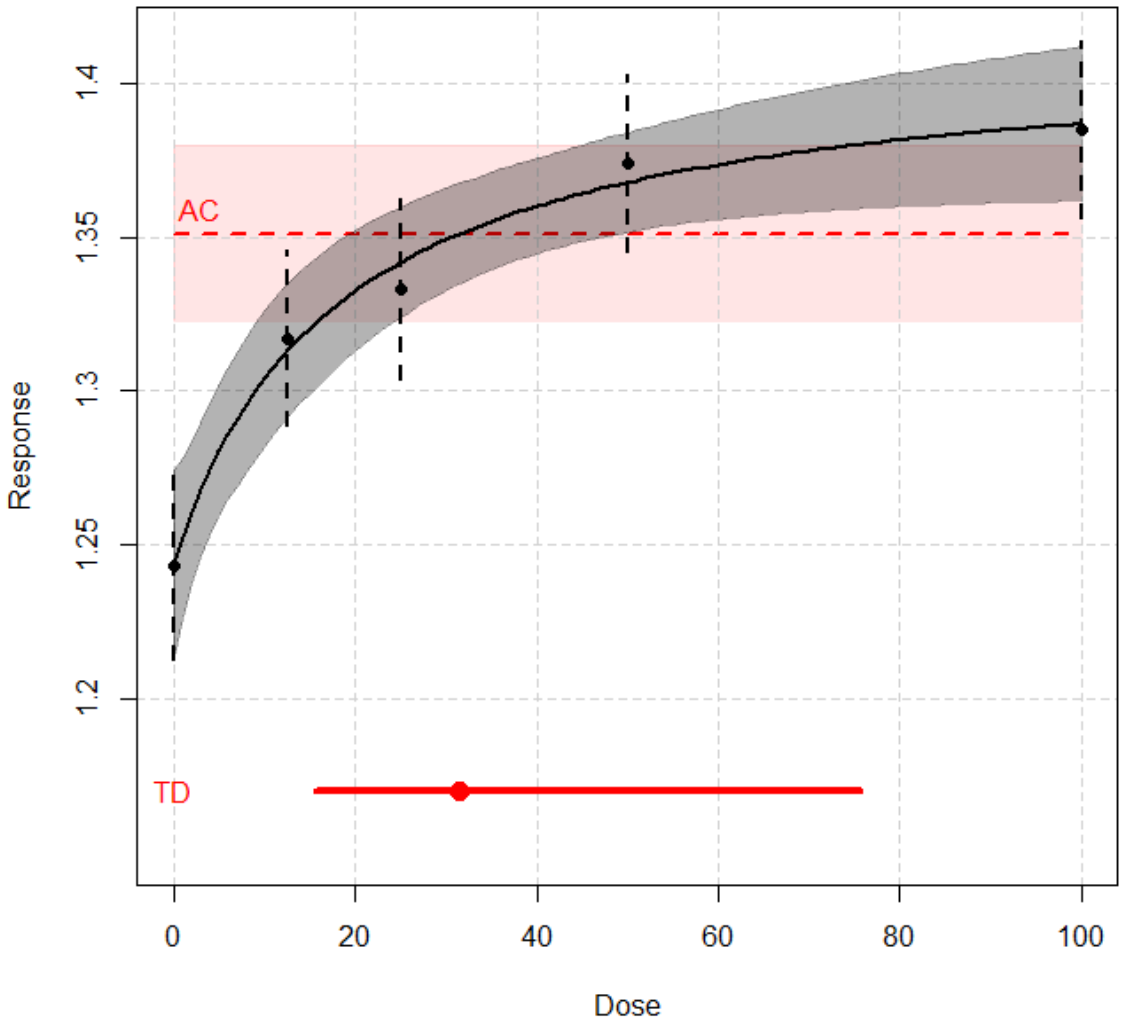
Dose-Finding Initiative

Model-based analysis



- Modelling provides more information
  - Smoothes dose estimates
  - Interpolation between doses
  - Confidence intervals for quantities of interest (dose achieving same effect as comparator (TD) etc)
- Modelling often only done as supportive analysis
  - Studies not designed for this purpose
- Issues with modelling
  - Pre-specification of one dose-response model at trial design stage difficult
  - No rigid pre-specification of how models are selected (potentially overfitting data)

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Dose-Finding Initiative

Start of informal dose-finding initiative (~2002)

- Try to get statistical objectives closer to the „real“ objectives
  - dose-response modelling techniques considered more adequate
  - this will have an impact on the study design:
    - Study potentially more doses (with less patients per dose), wider dose-range, ...
- Dose-Finding Initiative mandated by Biostatistics Management
  - worked on initially by members of the statistical methodology group within Novartis
  - later branching out to the general statistics group
  - (in parallel there was a group working on improving Phase I dose-finding designs: see Neuenschwander (2008), Statistics in Medicine, 27, 2420-39)

Dose-Finding Initiative

- First action items (2002/2003)
  - Identify current practices, example trials, and problem or critical issues for dose finding in full development across different TAs via interview with group heads or designated contact person.
  - Initiate collaboration with protocol review committee
  - Literature review
  - Re-analysis of existing data from dose-finding trials
  - ...
  - Original aim was not necessarily to develop new methods, ...
    - but this is what happened

MCP-Mod methodology

Motivation for developing MCP-Mod

- Use more dose-response modelling for Phase IIb, but according to more rigorous statistical standards
  - Acknowledge model-uncertainty
    - specify candidate set of models and how models are selected (or averaged) at design stage of the trial
  - Use procedure built from two parts
    1. MCP-part
       - trend tests for a dose-response trend (using the candidate shapes)
    2. Mod-part
       - fitting nonlinear/linear dose-response models and perform model based inference
    - combines the two traditional approaches towards dose-finding studies („best of both worlds“)

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

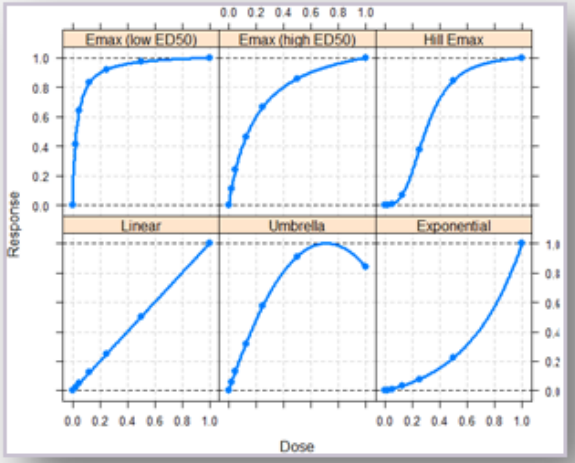
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



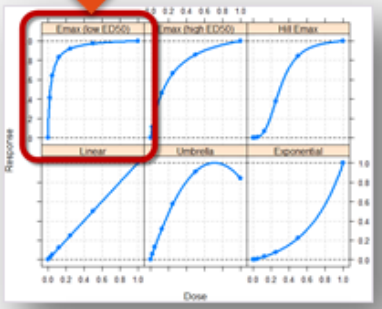
Trial conduct

$p < \alpha$?

Trial Analysis Stage

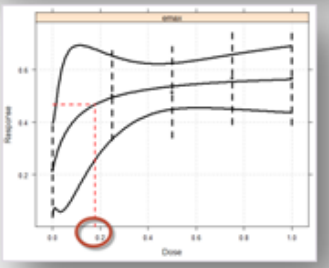
MCP step

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



Mod step

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



How to get it implemented in trials?

Internal Focus

- Biostatistics Organization
  - Important to get „lead“ statisticians on board
    - with review roles e.g., supervising trial statisticians, or statisticians on the clinical science review boards (review all projects before they get implemented)
    - often MCP-Mod got into projects through this route
  - Statisticians on project teams are the ones to implement method
    - They are involved in discussions with clinical teams and more senior decision makers
    - Need to get them „on board“: Need for support and technical enabling (see later)
  - Initiative originally mandated by management
    - awareness on management level helpful
      - but there was no mandate for trial statisticians to use particular methods

How to get it implemented in trials?

Internal Focus

- Cross-functional initiatives on how to improve dose-finding
  - 2004: Delphi initiative (in response to FDA critical path initiative)
    - Decision makers from all areas (clinical, safety, M&S, biostatistics, ...) develop ideas to modernize drug development
  - 2007: „Get the dose right“ (driven all major groups involved in clinical development)
  - 2011: Collaboration with M&S group on training for clinical decision makers
  - various presentations to non-statistical groups during the years

How to get it implemented in trials?

Technical Enabling

- Technical training of statisticians
  - Training sessions in 2005 & 2006 for all statisticians on MCP-Mod & dose-finding in general (repeated in 2011)
- Hands-on support for statisticians
  - Support in discussions with clinical team, writing protocol, writing analysis plans, software implementation
    - First studies: MCP-Mod as supportive analysis (~2004?), MCP-Mod as primary analysis (~2005/2006?)
- Providing software
  - 2005: Validated S-Plus library
  - since ~2007: SAS macros available
  - 2010: DoseFinding R package with methodology beyond MCP-Mod
- Work on further methodological aspects

How to get it implemented in trials?

External Focus

- Publishing papers
  - Feedback and from the scientific community,
    - main paper: Bretz et al. (2005), Biometrics, 61, 738-48
  - Independent, external & scientific validation of methodology
    - increases objective credibility of methodology
- Being part of across industry initiatives
  - PhRMA group on adaptive dose-finding studies (2005-2010) in response to FDA critical path initiative
  - Published white papers (2007, 2010): Discussed by regulatory statisticians (with rather positive feedback)
- giving external short courses (~ 6-8 throughout the years)
  - attended by statisticians from academia, industry and regulatory

How to get it implemented in trials?

Other important factors

- Internal case-studies powerful to convince non-statisticians
  - Two cases where traditional dose-finding „went wrong“
  - „Get the dose right“ training for whole Novartis Development (primary driver: M&S group)
    - any Pharma development associate would know about the topic
    - good starting point for discussions in clinical teams

Remarks

- Sounds more planned & smooth than it actually was
  - 3 different Biostatistics Department heads
  - 4 different Pharma Development heads
  - only at the beginning was a „formal“ initiative
    - there was always a team feeling responsible (& regarded as responsible) for the topic
    - this would get involved in more formal initiatives (internal, external)
  - People supporting the initiative changed through the years
    - none of us was part of the team when it started in 2002
    - other major contributors : José Pinheiro & Mike Branson

Remarks

- Key aspects (in hindsight)
  - having a core team being able to spend time on this continuously
    - supported by the Biostatistics group management in different forms throughout the years
  - Focus on internal but at the same time external focus, involving scientific community & regulators in the process
    - external activities can result in powerful arguments to use for internal influencing

References

- EMA qualification opinion on MCP-Mod

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/02/WC500161027.pdf

- Request for EMA qualification opinion
  - contains a good overview on MCP-Mod and all relevant literature references

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/10/WC500152302.pdf