Changing the culture in drug development: The need to implement innovative scientific solutions

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Acknowledgment: Jean-Louis Steimer (Novartis)

IDEAS Dissemination Workshop

September 26, 2018 – Basel

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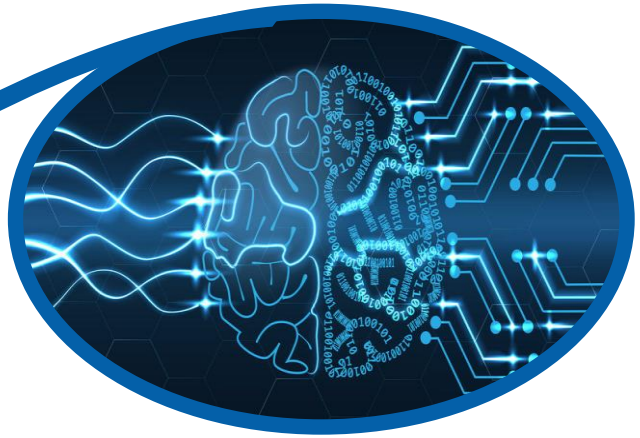
Constant need to drive for innovative scientific solutions

Advances in technology



More complex data

Leverage data to support quantitative decision making

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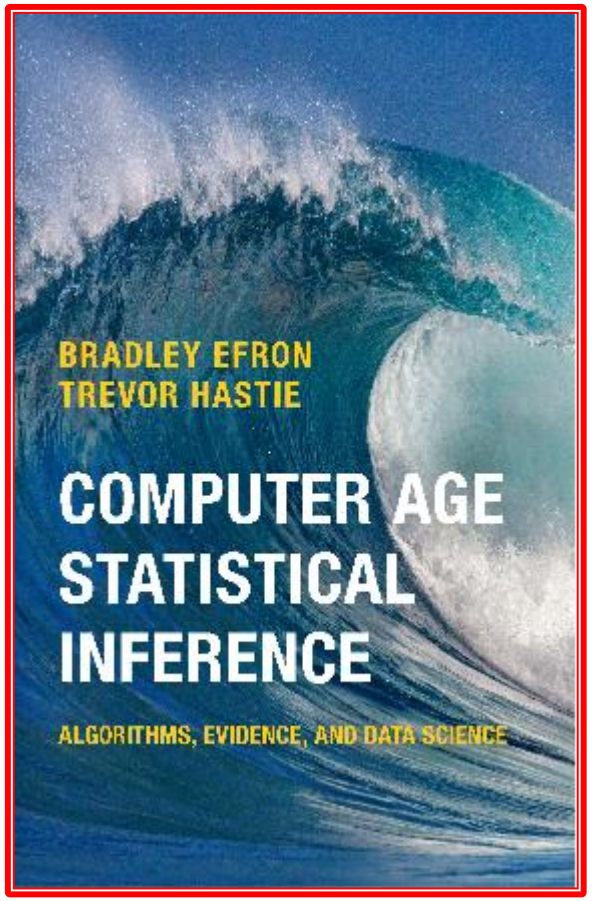
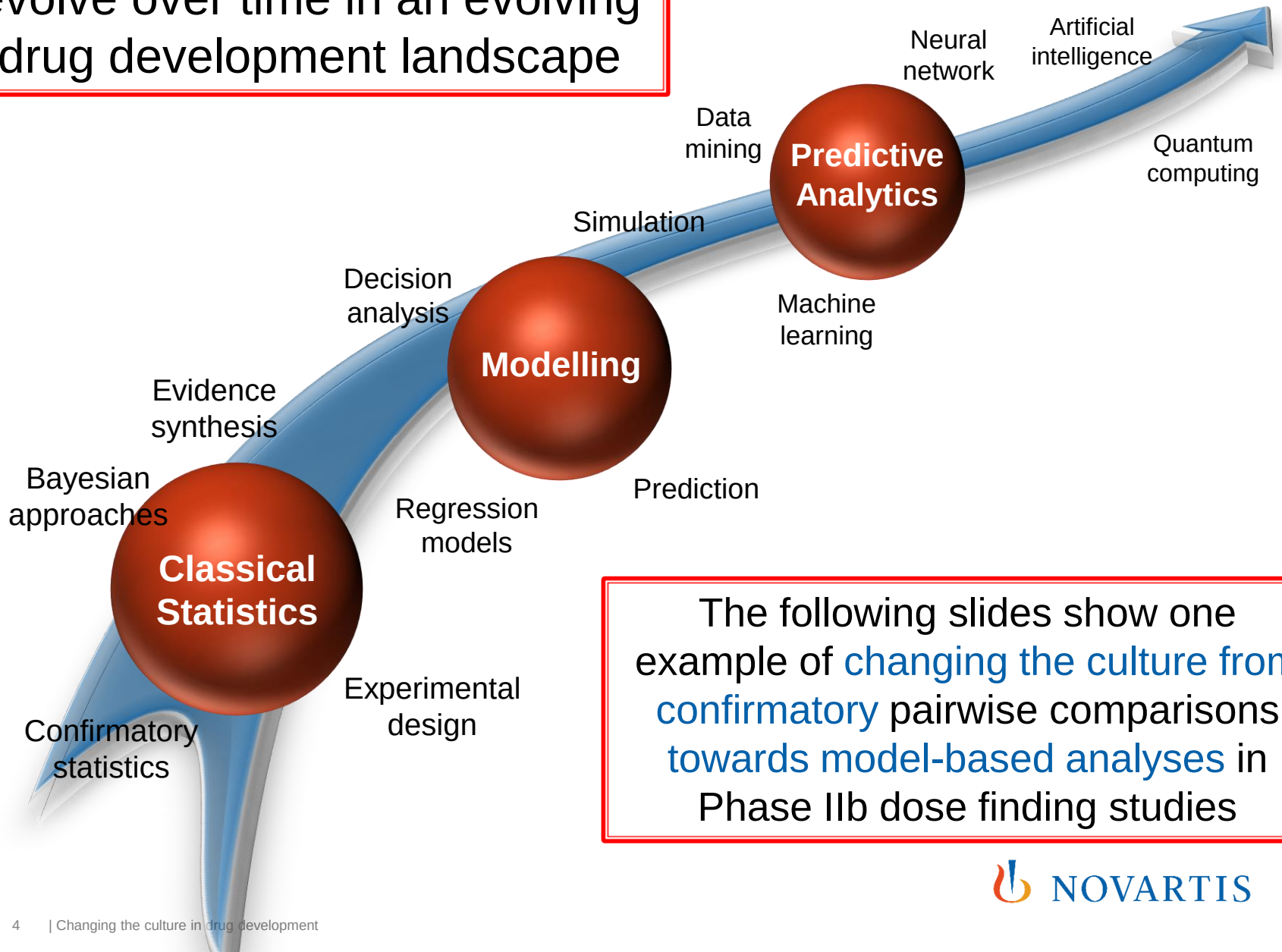


- Part I Classic Statistical Inference
- Part II Early Computer-Age Methods
- Part III Twenty-First-Century Topics

Quantitative solutions and tools evolve over time in an evolving drug development landscape



The following slides show one example of changing the culture from confirmatory pairwise comparisons towards model-based analyses in Phase IIb dose finding studies

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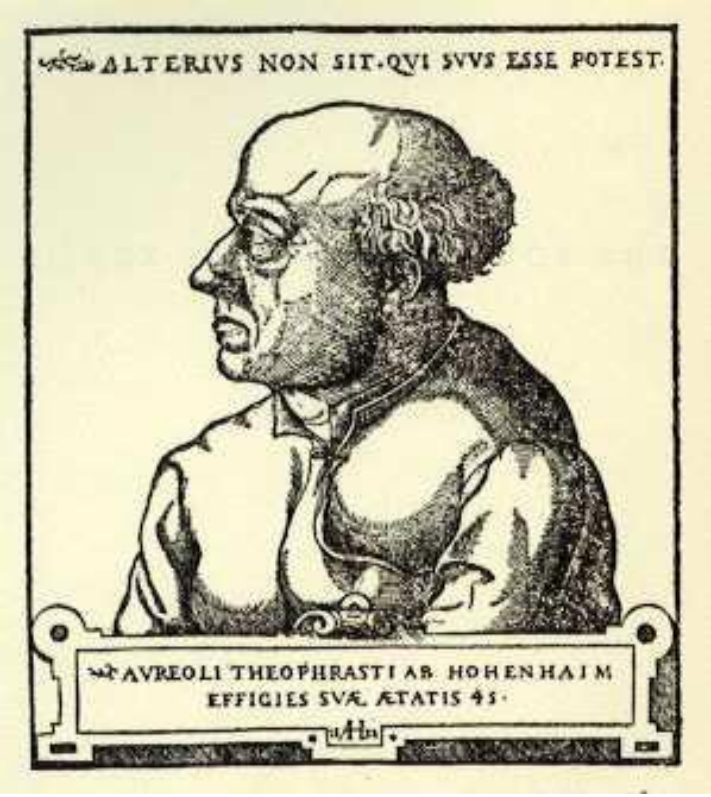
Dose finding

Paracelsus (1493 – 1541)



All things are poison and nothing is without poison, only the dose permits something not to be poison.

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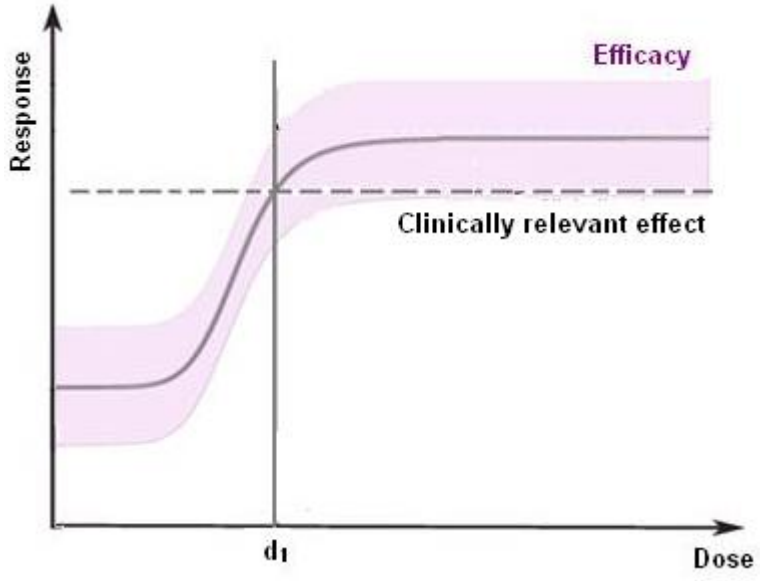
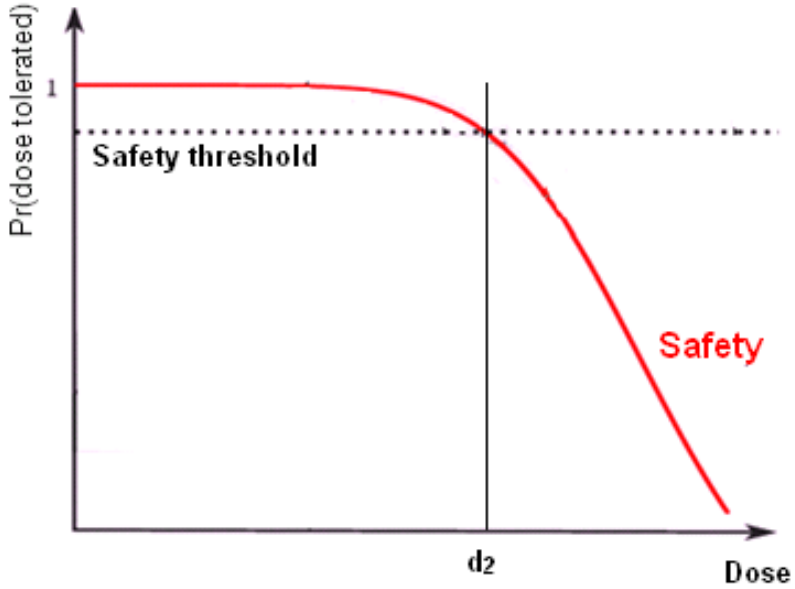
Dose finding

Objectives

- Characterizing dose response for safety and efficacy is critical:
  - If a dose is too high, safety and tolerability problems are likely to result
  - Too low a dose may lead to inadequate efficacy
- Therapeutic window: doses that are both efficacious and safe
- Optimal dose: a trade-off between efficacy and safety





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ICH E4

Main regulatory guidance on dose response studies

European Medicines Agency

November 1994
CPMP/ICH/378/95

ICH Topic E 4
Dose Response Information to Support Drug Registration

Step 5

NOTE FOR GUIDANCE ON DOSE RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION
(CPMP/ICH/378/95)

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Selecting the right dose

Are we doing ok?

- Paracelsus: ~ 500 years ago
- ICH E4: ~ 25 years ago

We are doing ok now.

Right?

21% of drugs filed in 1980 – 1999 had post-approval dosage changes or were removed from sale (Cross et al., 2002)

In the 2000 – 2012 cohort, ~ 16% of submissions to FDA that failed to be approved first time were due to uncertainties related to dose selection (Sacks et al., 2014)

We are doing ok now.

This talk

Summary

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

  2003

  - Developed by Novartis Statistics group to improve dose finding practices

  2016

  - Method is now used in most Phase IIb dose finding studies at Novartis (when appropriate) as well as by other major pharmaceutical companies
  - Acknowledged in 2014 through a positive Qualification Opinion by the European Medicines Agency (EMA)
    - First time that a regulatory agency formally endorsed a clinical trial methodology
  - Acknowledged in 2016 through a Fit-for-Purpose Determination by the U.S. Food and Drug Administration (FDA)

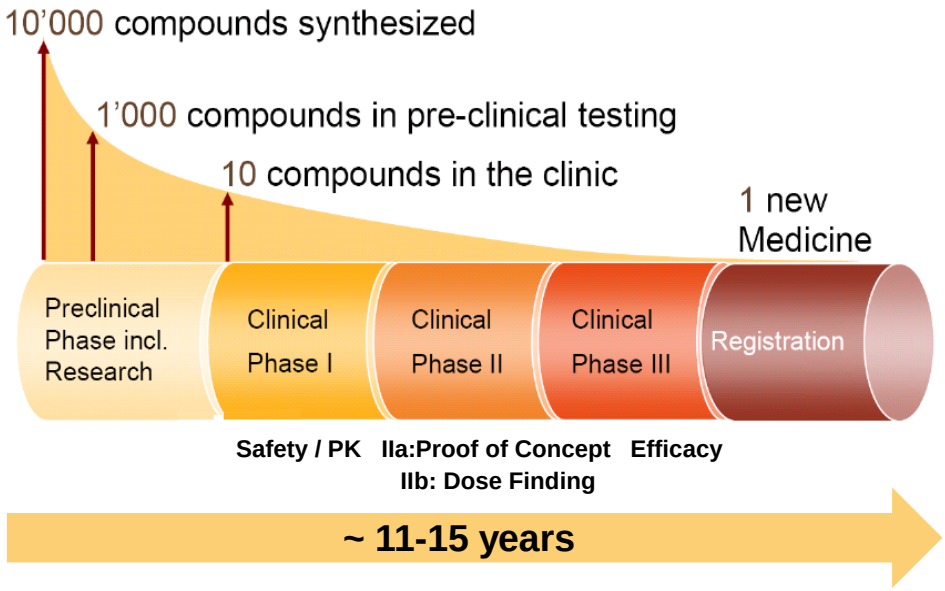
- This presentation is about what happened in between

Outline

- Drug development environment
- MCP-Mod story
  - Starting point: Biostatistics Dose Finding Initiative
  - Brief non-technical description of MCP-Mod methodology
  - How we got it implemented in clinical trials
    - Internal and external focus
    - Technical enablement
  - Remarks

Drug development environment

A regulated environment



- After end of Phase III
  - Regulatory agencies review quality, safety and efficacy of new drug applications and eventually grant market approval
  - Innovation needs to convince not only decision makers within the company but also regulatory bodies and other stakeholders

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Drug development environment

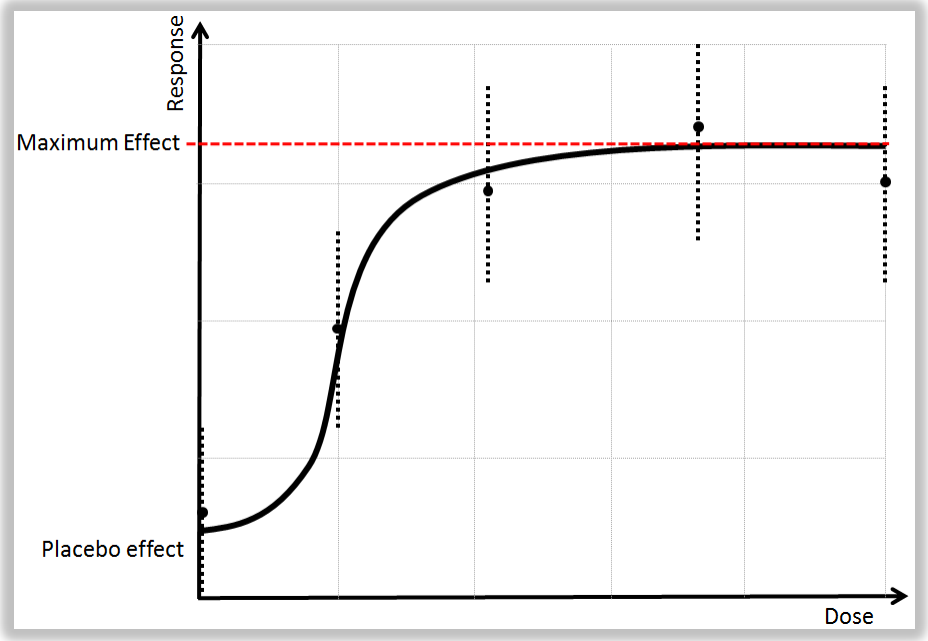
A regulated environment

- A regulatory opinion on an innovative solution is not always immediately 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)
    - ... despite the fact that regulators support innovation in different ways, 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 about benefits of the new approach
  - Tendency towards standardization of work flows. Innovation challenges existing standards and requires re-thinking (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?

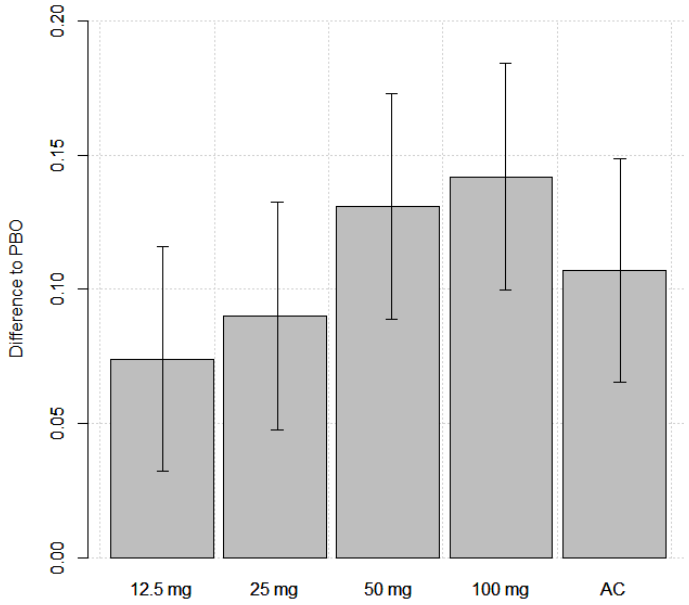


- Safety / tolerability dose response curve to be considered as well
- Ultimate aims
  - Be able to make reliable go / no-go decision when entering Phase III
  - If we go, which dose(s) to choose, i.e. which doses (or regimen) have the best benefit-risk relationship?

Motivation to improve Phase II dose finding

Start of informal dose finding initiative (~2002)

- Mismatch between real study objectives and objectives in protocol
  - Statistical objectives in protocols would focus on hypotheses testing, typically pairwise comparisons of active doses against control
  - Study design determined by such objectives, e.g. sample size, number of doses (typically kept at a minimum), dose levels being used, ...
- Example output of a pairwise analysis



- Conclusions
  - All active doses and the active comparator (AC) are significantly different from placebo
- What happens between observed doses?
- What is the dose response curve?
- Which dose(s) give same effect as AC?

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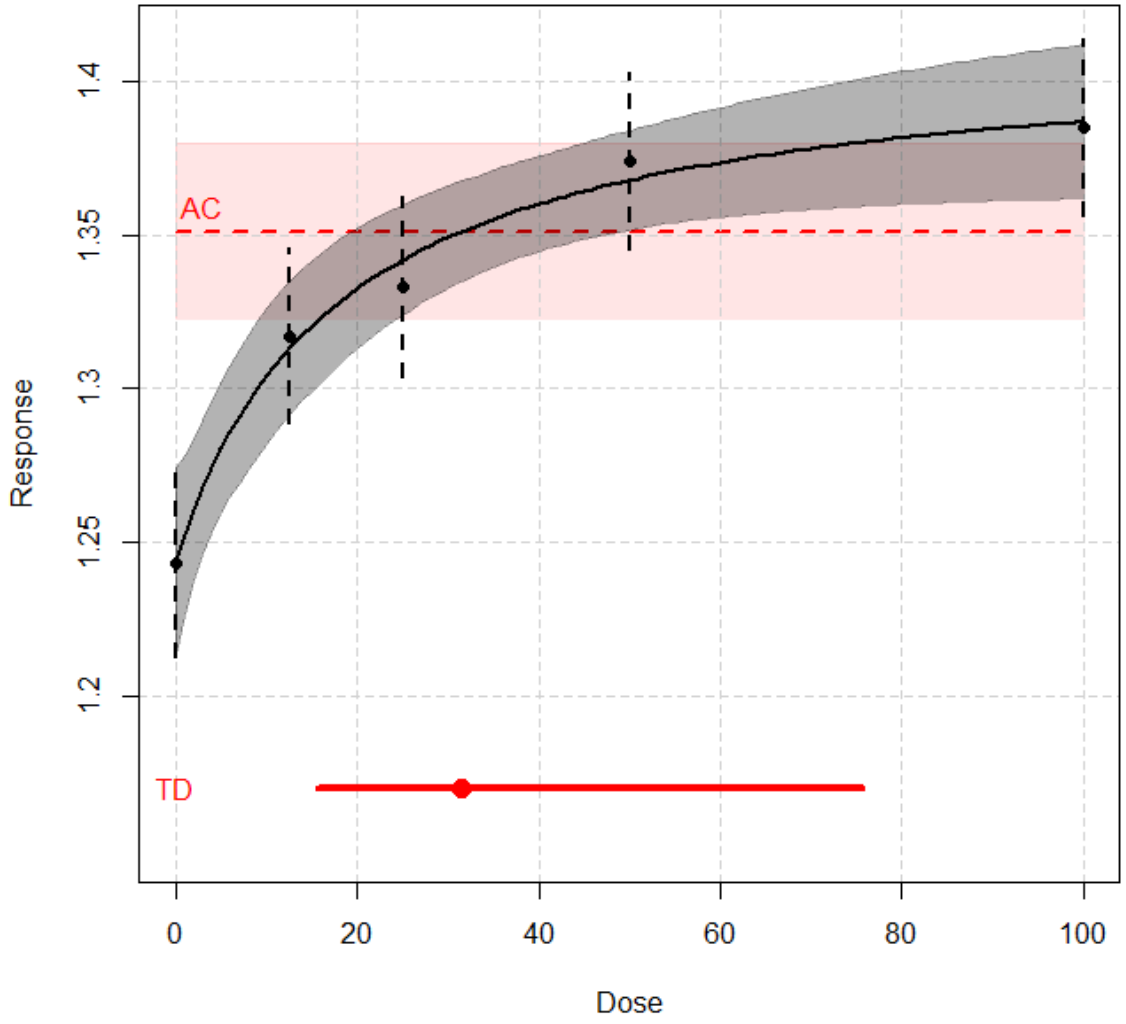
Dose Finding Initiative

Model-based analysis



- Modelling provides more information
  - Smoothes dose estimates
  - Interpolation between doses
  - Confidence intervals for quantities of interest, e.g. target dose (TD) achieving same effect as AC
- Modelling often only done as supportive analysis
  - Most 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 match statistical objectives with the real study objectives
  - Dose response modelling techniques considered to be more adequate
  - With potential consequences for study designs, e.g. investigate more doses (with less patients per dose), wider dose range, ...
- Dose Finding Initiative started by Biostatistics Management
  - Initially with sole contributions from members of the Statistical Methodology group at Novartis
  - Later branched out into the broader Biostatistics group
  - In parallel a working group was initiated to improve Phase I dose finding
    - See, for example, Neuenschwander et al. (2008), Statistics in Medicine 27, 2420-39

Dose Finding Initiative

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

MCP-Mod methodology

Motivation for developing MCP-Mod

- Use more dose response modelling in Phase IIb, but according to more rigorous statistical standards
  - Acknowledge model uncertainty
    - Specify at design stage a candidate set of dose response models and how models are selected (or averaged)
  - Led to a procedure based on two parts
    1. MCP part: trend tests for dose response signal detection using candidate dose response models elicited at the design stage
    2. Mod part: fit nonlinear / linear dose response models and perform model based inference
  - MCP-Mod combines both traditional approaches based on testing and modelling, tailored to dose finding studies („best of both worlds“)

MCP-Mod

A unified dose finding approach

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

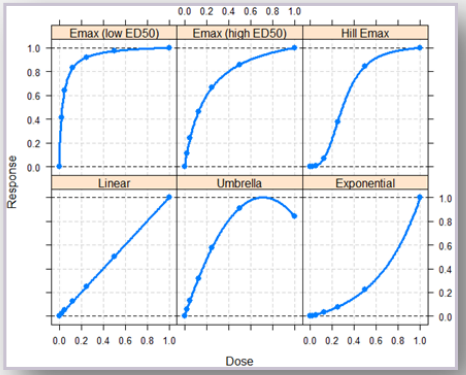
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



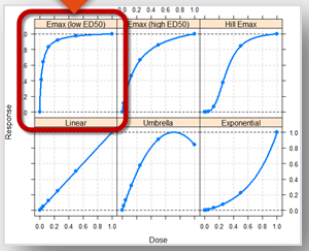
Trial conduct

p < α?

Trial Analysis Stage

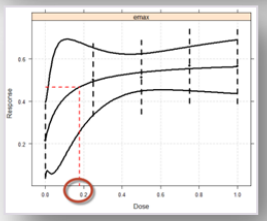
MCP step

- 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)



MCP-Mod

Broadly used across many therapeutic areas (2013)

Study ID	Phase	Condition studied	Treatment groups
ACZ885H2255	Phase IIb	Gout	5 doses, AC
ACZ885I2202	Phase IIb	Diabetes	PBO, 4 doses
ACZ885M2301	Phase III	Prevention of cardiovascular events	PBO, 3 doses
ACZ885M2301S1	Phase III	Prevention of cardiovascular events	PBO, 3 doses
ACZ885M2301S2	Phase III	Prevention of cardiovascular events	PBO, 3 doses
AEB071C2201	Phase IIb	Psoriasis	PBO, 3 od and 4 bid doses
BAF312A2201	Phase IIb	Multiple Sclerosis	PBO, 5 doses
BGG492A2207	Phase IIa/b	Epilepsy	PBO, 2 doses
LCI699A2201	Phase II	Hypertension	PBO, 3 od doses, 1 bid dose
LCQ908A2203	Phase IIb	Diabetes	PBO, 5 doses, AC
LCQ908B2302	Phase III	Familial Chylomicronemia Syndrome	PBO, 2 doses
LCQ908C2201	Phase II	Hypertriglyceridemia	PBO, 3 doses, 2 AC
LCZ696A2201	Phase IIb	Hypertension	PBO, 3 doses, 3 AC
LIK066A2202	Phase IIb	Diabetes	PBO, 7 doses
NVA237A2205	Phase IIb	COPD	PBO, 4 od doses, AC
NVA237A2208	Phase IIb	COPD	PBO, 3 bid doses, 4 od doses
QAW039A2206	Phase IIb	Asthma	PBO, 9 od doses, 4 bid doses, AC
QMF149B2201	Phase II	COPD	PBO, 4 doses
SAF312A2103	Phase IIa	Dental pain	PBO, 6 doses, AC
XBD179A2204	Phase II	Generalized anxiety disorder	PBO, 4 doses

PBO = Placebo
AC = Active Control

How did we get it implemented in trials?

Internal focus

- Biostatistics organization
  - Important to engage senior / lead statisticians
    - With strategic 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 the method
    - They are involved in discussions with clinical teams and more senior decision makers
    - With the aim to engage them, the need for technical enablement was raised (see later)
  - Initiative originally started by management
    - Awareness on management level helpful, but there was no mandate for trial statisticians to use any particular method

How did we get it implemented in trials?

Internal focus

- Cross-functional initiatives to improve dose finding practices
  - 2004: DELPhI initiative in response to FDA Critical Path Initiative
    - Senior representatives from different line functions (clinical, safety, M&S, statistics, ...) developed conceptual ideas to modernize drug development
  - 2007: „Get the dose right“ project driven by Modeling & Simulation (M&S) department
    - High-level training rolled out broadly across Development organization
    - Any Development associate would be educated about this topic
    - Good starting point for discussions in clinical teams
  - 2011: Collaboration with M&S on training for clinical decision makers
  - Various presentations to non-statistical groups during the years

How did we get it implemented in trials?

Technical enablement

- Technical training for statisticians
  - Global training sessions rolled out in 2006 on MCP-Mod and dose finding in general (updated and repeated in 2011 and 2015)
- Hands-on support for statisticians
  - Support in discussions with clinical team, writing protocol and analysis plans, software implementation
    - First studies completed: MCP-Mod as supportive analysis (~2004?) and as primary analysis (~2005/2006?)
- Software implementation
  - 2005: Validated S-Plus library
  - since ~2007: generic SAS macros available
  - 2010: DoseFinding R package on CRAN (beyond MCP-Mod)
  - 2015: ADDPLAN DF, PROC MCPMOD

How did we get it implemented in trials?

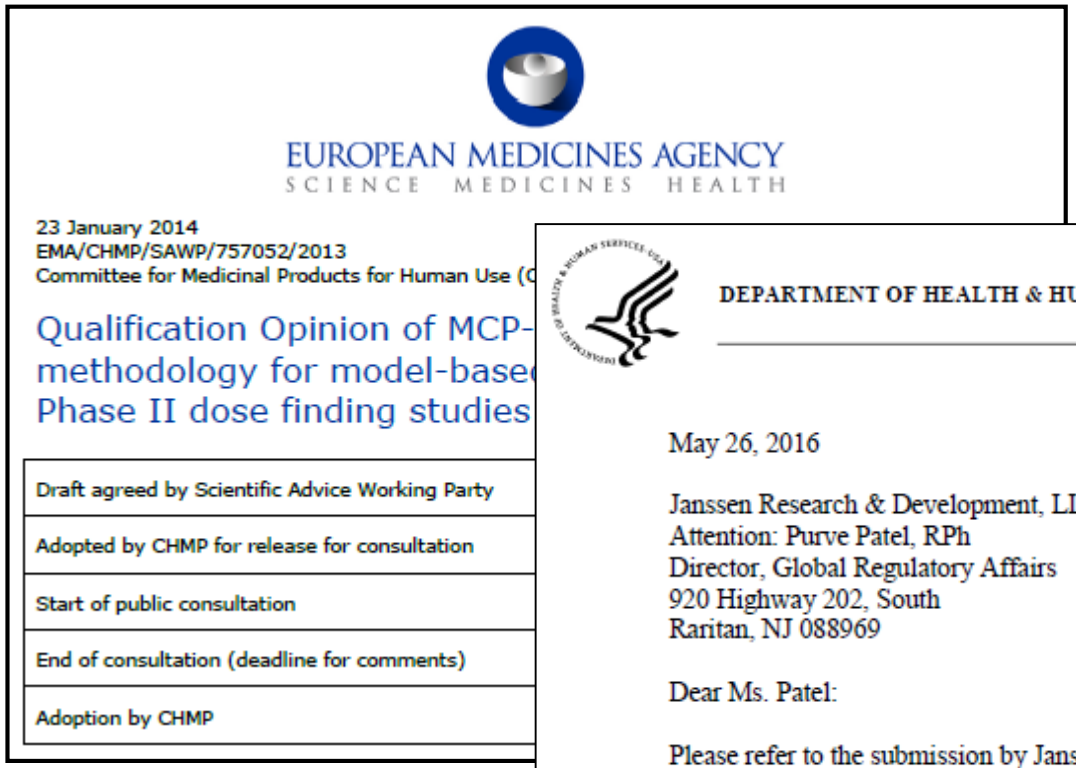
External focus

- Continuous work on methodological questions
  - Extension of original methodology, experience-sharing through published case studies and feedback from the scientific community
    - Main paper in 2005, approximately 15 papers in total over the years
  - Independent, external and scientific validation of methodology
    - increases objective credibility of methodology
- Being part of cross-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 encouraging positive feedback)
- External short courses (>10 throughout the years)
  - Attended by statisticians from academia, industry and regulatory

How did we get it implemented in trials?

External focus

- Qualification opinion by EMA in 2014
- Fit-for-Purpose Determination by FDA in 2016

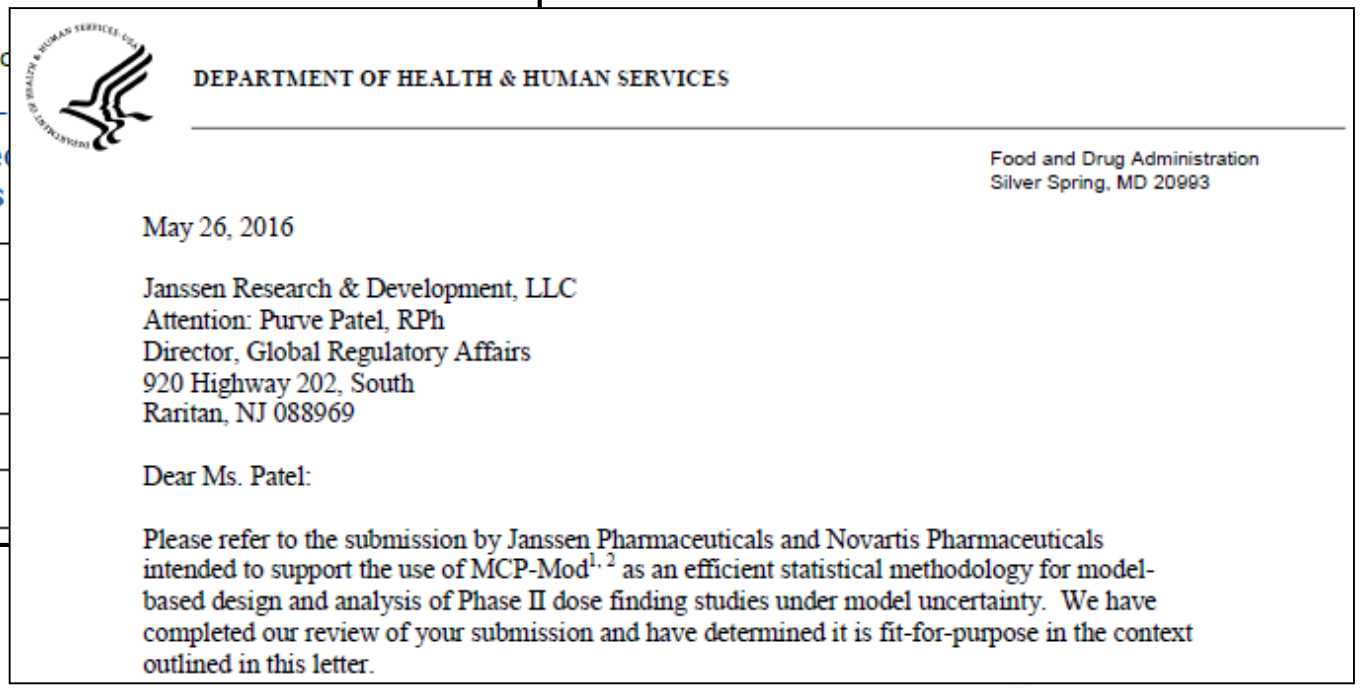


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Qualification Opinion of MCP-
methodology for model-base
Phase II dose finding studies

Draft agreed by Scientific Advice Working Party
Adopted by CHMP for release for consultation
Start of public consultation
End of consultation (deadline for comments)
Adoption by CHMP



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

May 26, 2016

Janssen Research & Development, LLC
Attention: Purve Patel, RPh
Director, Global Regulatory Affairs
920 Highway 202, South
Raritan, NJ 088969

Dear Ms. Patel:

Please refer to the submission by Janssen Pharmaceuticals and Novartis Pharmaceuticals intended to support the use of MCP-Mod[1, 2] as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. We have completed our review of your submission and have determined it is fit-for-purpose in the context outlined in this letter.

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Year	Internal		External
	Strategy	Enabling	
2002	• Biostatistics “Dose Finding Project” for Early and Full Development • Initial ideas for MCP-Mod		
2003			
2004	• DELPhI initiative		• FDA Critical Path initiative
2005		• Development of internal validated S-Plus library MCP-Mod	• Publication: Original MCP-Mod (Biometrics) • PhRMA working group • First use of MCP-Mod outside Novartis (Naitee Ting at Pfizer)
2006	• Completion of first study at Novartis with MCP-Mod as primary analysis	• Two-day training on MCP-Mod (Europe, US) • Development of protocol template	
2007	• Cross-functional initiative “Get the dose right”		• PhRMA White Paper
2008		• Development of MCP-Mod SAS macros	• Publication: MCPMod R package

Year	Internal		External
	Strategy	Enabling	
2009	• New Horizon Award • Honorable mention in the Innovation category of the Pharma CEO Award		
2010		• Development of DoseFinding R package	• Publication: DoseFinding R package (includes MCP-Mod)
2011	• Development of advanced training course	• Two-day training on MCP-Mod (Europe, US)	
2012	• Co-development of ADDPLAN DF started		
2013			• RSS/PSI Award for Statistical Excellence in the Pharmaceutical Industry
2014			• Publication: generalized MCP-Mod (SiM) • CHMP Qualification Opinion
2015	• New dose-finding initiative started, with expanded focus	• One-day internal training on ADDPLAN DF (Europe, US, China)	• Publication: MCP-Mod SAS macros • PROC MCPMOD under development

Remarks

- Sounds more planned and smooth than it actually was
  - 4 different Biostatistics Department heads
  - 5 different Pharma Development heads
  - Only at the beginning it was a „formal“ initiative
    - There was always a team taking ownership for the topic and given the necessary ownership
    - This team would get involved in more formal initiatives (internal, external)
  - People contributing to the initiative changed through the years
    - Original lead by José Pinheiro and Mike Branson when it started in 2002
    - Others joined the team over time, sometimes staying only for a brief period

Remarks

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

Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has.

Margaret Mead

Thank You

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