

Panel Discussion

Modelling and Simulation and the Regulatory Process

6th June 2012, 9:00 – 10:15

Chair: Joachim Grevel, BAST Inc Limited

European Medicines Agency-European Federation of
Pharmaceutical Industries and Associations

EMA-EFPIA Modelling and Simulation Workshop

30/11/2011 - 01/12/2011

All the presentations and reports are now available in the EMA website:

http://www.emea.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3

Today we discuss the following questions:

1. Why is the concept of the target concentration not guiding drug development during all clinical phases? And why are regulators not asking for the corresponding dosing target to guide therapy?
2. How does one rationally select a dose in the absence of having characterised a dose response?
3. If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?
4. Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?
5. It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and how can EFPIA help?

Time	Topic/Speaker	slides
5 min	Summary of workshop by Terry Shepard	 Microsoft oint 97-2003 Prese
5 min	Summary of workshop by Peter Milligan	 EFPIA position
5 min	Questions: Leon Aarons	 Microsoft Office erPoint 2007 Pres
5 min	Questions: Nick Holford	 Microsoft Office erPoint 2007 Pres
5 min	Questions: Peter Milligan	 Microsoft Office erPoint 2007 Pres
5 min	Questions: Gerard Pons	 Microsoft Office erPoint 2007 Pres
5 min	Questions: Mick Looby	 Microsoft oint 97-2003 Prese
5 min	Questions: Terry Shepard	 Microsoft oint 97-2003 Prese

Open Discussion: GO!

1. Why is the concept of the target concentration not guiding drug development during all clinical phases? And why are regulators not asking for the corresponding dosing target to guide therapy?
2. How does one rationally select a dose in the absence of having characterised a dose response?
3. If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?
4. Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?
5. It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and how can EFPIA help?

Summary by Terry Shepard of the MS workshop at EMA



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Role of Modelling and Simulation in Regulatory Decision Making in Europe

Terry Shepard

Medicines and Healthcare products Regulatory Agency

Shortened Version of Presentation of November 30, 2011

EMA, London

For the PAGE 2012 Meeting, Venice

June 6th, 2012

An agency of the European Union





Disclaimer

The views expressed in this presentation are the harmonised views of experts across a number of European regulatory agencies and EMA, but do not necessarily reflect the official EMA position or that of its committees or working parties.



Overview

Framework for M&S in regulatory review

Vision for the future

Conclusions



Framework for M&S in Regulatory Review

According to impact on regulatory decision

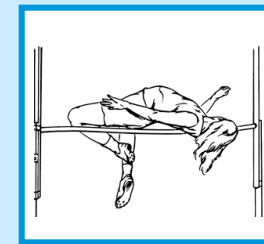
High impact

Scientific Advice, Supporting Documentation, }
Regulatory Scrutiny } +++



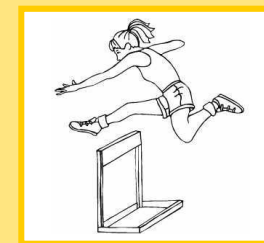
Medium impact

Scientific Advice, Supporting Documentation, }
Regulatory Scrutiny } ++



Low impact

Scientific Advice, Supporting Documentation, }
Regulatory Scrutiny } +



Impact on regulatory decision



Framework for M&S in Regulatory Review

According to impact on regulatory decision

EXAMPLES

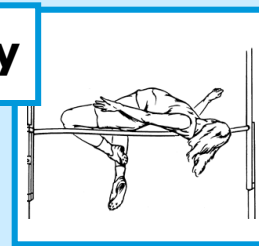
High impact

- Extrapolation of efficacy and safety from limited data (e.g. term and preterm neonates, paediatrics, small populations)
- Model-based inference of efficacy/safety in lieu of pivotal clinical data

Replace

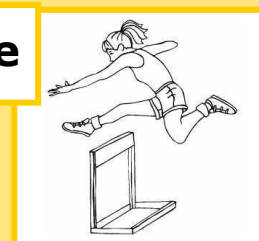
Medium impact

- Identify safe and efficacious exposure range (exposure-response in target population)
- Justify not doing a study (e.g. drug-drug interaction based on PBPK)

Justify

Low impact

- Internal decision making (hypothesis generation, learning)
- Verify conclusions drawn from preclinical observations and PK data in healthy volunteers

Describe

Impact on regulatory decision



The Future: Is the role of M&S in regulatory decision making evolving?

Decrease late stage failures

Maximise information from limited patient numbers (paediatrics, orphan drugs)

+ older patients

Mechanistic models for DDIs, pharmacogenetic effects, PK, PD, safety

Qualification of novel methodologies/biomarkers

Application to safety biomarkers

Confirmatory studies

- Disease progression models for design of phase 2 and 3 studies
- More efficient trial designs, fewer trials (single pivotal trial), shorter development programmes
- Model based analysis of primary clinical endpoints, supporting and enriching primary analysis

MBDD → MIMAA

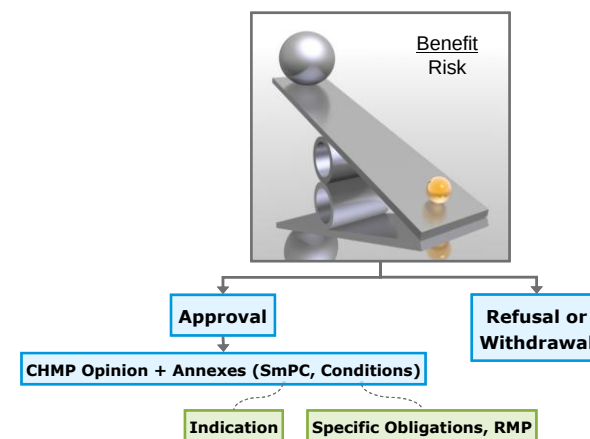


Conclusions

Endorse and support growth of M&S applications to quantify information, inform decision-making, design trials ...

M&S supports best informed outcome of risk benefit decisions

- MBDD → MIMAA
- M&S in response to questions raised during assessment
- Scientific advice, documentation according to impact on risk benefit decision



Lack of M&S/quantitative pharmacology misses opportunity to mitigate uncertainty with potential impact on indication, post-approval burden, etc.



Conclusions

Dialogue will be key to extending /
expanding use to agree viable objectives
and assumptions and to agree
documentation required.



Acknowledgements

Particular thanks to...

Monica Edholm, Siv Jönsson, Tomas Salmonson (MPA), Efthymios Manolis (EMA),
Rob Hemmings, Dan O'Connor (MHRA)

Thanks also to...

Gérard Pons (Saint Vincent de Paul Hospital)

Ralf Herold (EMA)

Marc Maliepaard (MEB)

Liesbeth Rook (MEB)

Martin Posch (EMA)

Filip Josephson (MPA)

Christoph Male (Medical University of Vienna)

Luca Pani (AIFA)

Christel Kamp (PEI)

Norbert Benda (Bfarm)

Peter Volkers (PEI)

Walter Janssens (Fagg-Afmps)

David Neil (MHRA)

Krishna Prasad (MHRA)

Markku Pasanen (University of Kuopio)

Beatriz Silva Lima (INFARMED, U. of Lisbon)

José Augusto Guimarães Morais (INFARMED,
University of Lisbon)

Jean-Marc Vidal (EMA)



References (Publications and Guidelines)

Publications

Siv Jönsson, Anja Henningsson, Monica Edholm, and Tomas Salmonson (2011). Contribution of Modeling and Simulation Studies in the Regulatory Review: A European Regulatory Perspective. In H.H.C. Kimko and C.C. Peck (eds.), *Clinical Trial Simulations, Applications and Trends*, AAPS Advances in the Pharmaceutical Sciences Series, 1st Edition (pp. 15-36). New York: Springer.

Efthymios Manolis & Gérard Pons. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. *Br J Clin Pharmacol* 68:4 / 493–501 (2009).

Efthymios Manolis and Ralf Herold. Pharmacometrics for Regulatory Decision Making, Status and Perspective. *Clin Pharmacokinet* 50: 625-626 (2011).

Efthymios Manolis, Tariq Eldirdiry Osman, Ralf Herold, Franz Koenig, Paolo Tomasi, Spiros Vamvakas & Agnes Saint Raymond. Role of modeling and simulation in pediatric investigation plans. *Pediatric Anesthesia* ISSN 1155-5645 (2010).

Guidelines

Guideline on clinical investigation of medicinal products for the treatment of sepsis. (CHMP/EWP/4713/03)

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. (CHMP/EWP/566/98 Rev. 2 Corr.)

Guideline on clinical trials in small populations. (CHMP/EWP/83561/2005)

Guideline on reporting the results of population pharmacokinetic analyses. (CHMP/EWP/185990/06)

Guideline on the clinical development of medicinal products for the treatment of HIV infection. (EMA/CPMP/EWP/633/02 Rev. 2)

Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease. (CHMP/EWP/1343/01 Rev. 1)

Guideline on the clinical evaluation of medicinal products intended for treatment of Hepatitis B. (CHMP/EWP/6172/03)

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. (CHMP/EWP/89249/2004)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. (CPMP/EWP/2339/02)

Guideline on the investigation of medicinal products in the term and preterm neonate. (EMA/536810/2008)

Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. (EMA/CHMP/EWP/147013/2004)



References (Publications and Guidelines)

Guidelines (continued)

ICH Topic E 11. Note for guidance on clinical investigation of medicinal products in the paediatric population. (CPMP/ICH/2711/99)

ICH Topic E 14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for NonAntiarrhythmic Drugs. (EMA/CHMP/ICH/310133/2008)

ICH Topic E 4. Note for guidance on dose response information to support drug registration. (CPMP/ICH/378/95)

ICH Topic E 7. Note for guidance on studies in support of special populations: geriatrics. (EMA/CHMP/604661/2009)

Note For Guidance On Modified Release Oral And Transdermal Dosage Forms: Section II (Pharmacokinetic And Clinical Evaluation) (CPMP/EWP/280/96/ Corr*)

Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. (CHMP/EWP/225/02)

Note for guidance on the investigation of drug interactions. (draft) (EMA/CHMP/EWP/125211/2010)

Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. (CPMP/EWP/2655/99)

Points to consider on application with 1.meta-analyses, 2.one pivotal study (CPMP/EWP/2330/99)

Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products. (EMA/128517/2006)

Proceedings of EMA/EFPIA Modelling and Simulation Workshop

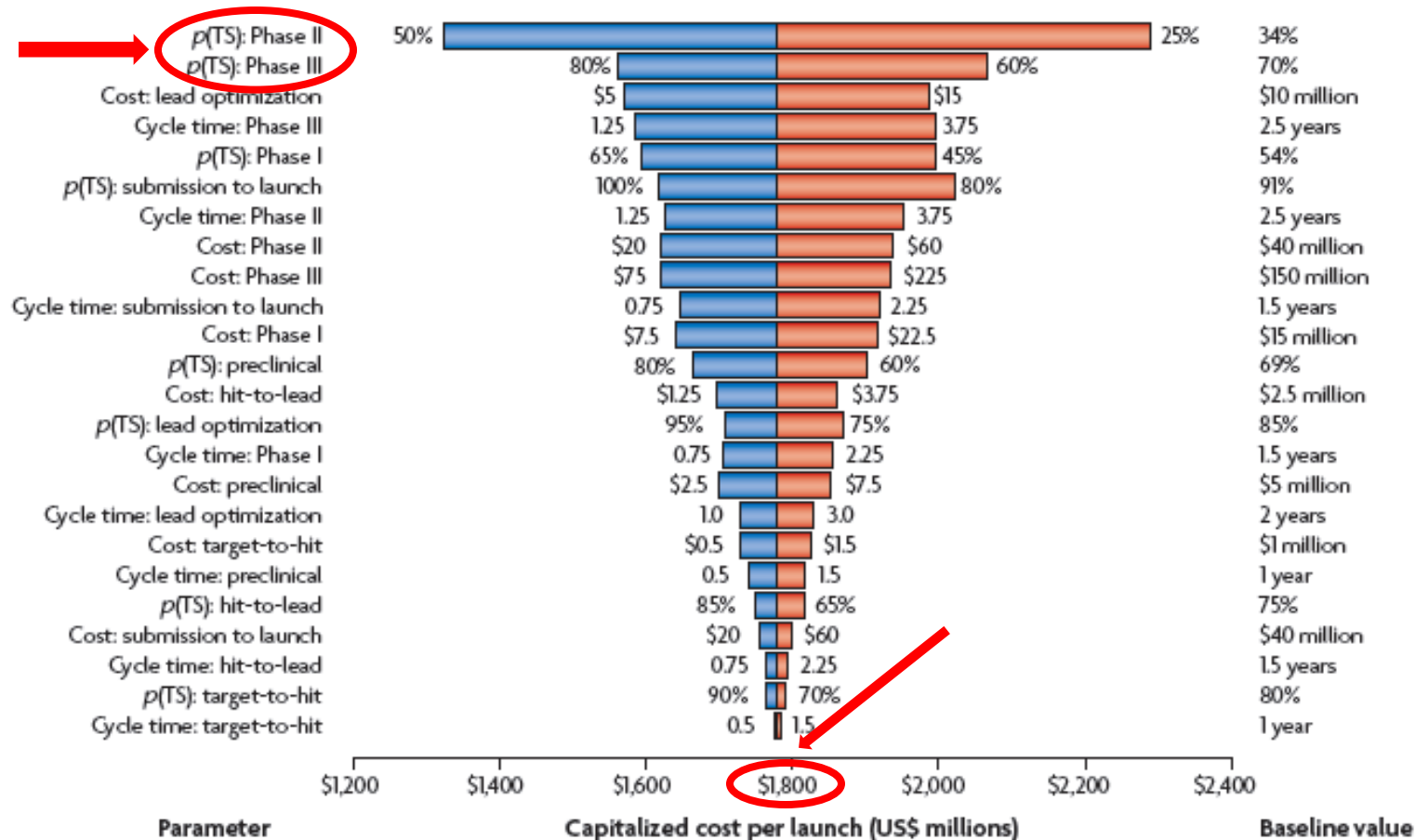
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3

Summary by Peter Milligan of the MS workshop at EMA

Current Position and Expectation for use of M&S in Drug Development and Regulatory Decision Making

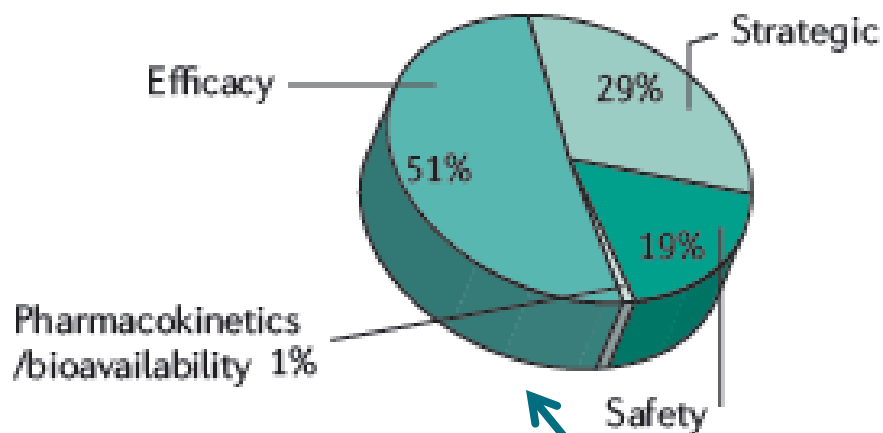
Peter A Milligan
(on behalf of EFPIA workshop contributors)

High Failure Rates in Phases 2 and 3 are the most Important Determinants of Drug Development Cost

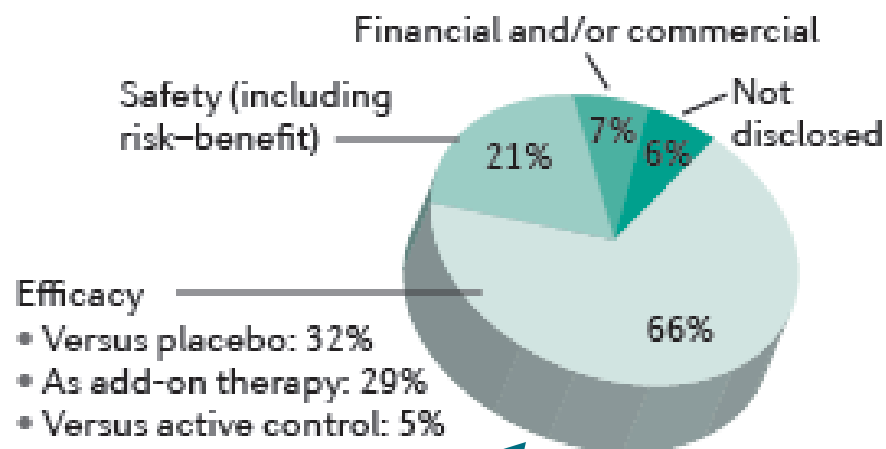


Causes of Failure in Phases 2 and 3

Phase 2 Failures: 2008 – 2010
(N = 87 compounds)



Phase 3 Failures: 2007 – 2010
(N = 83 compounds)

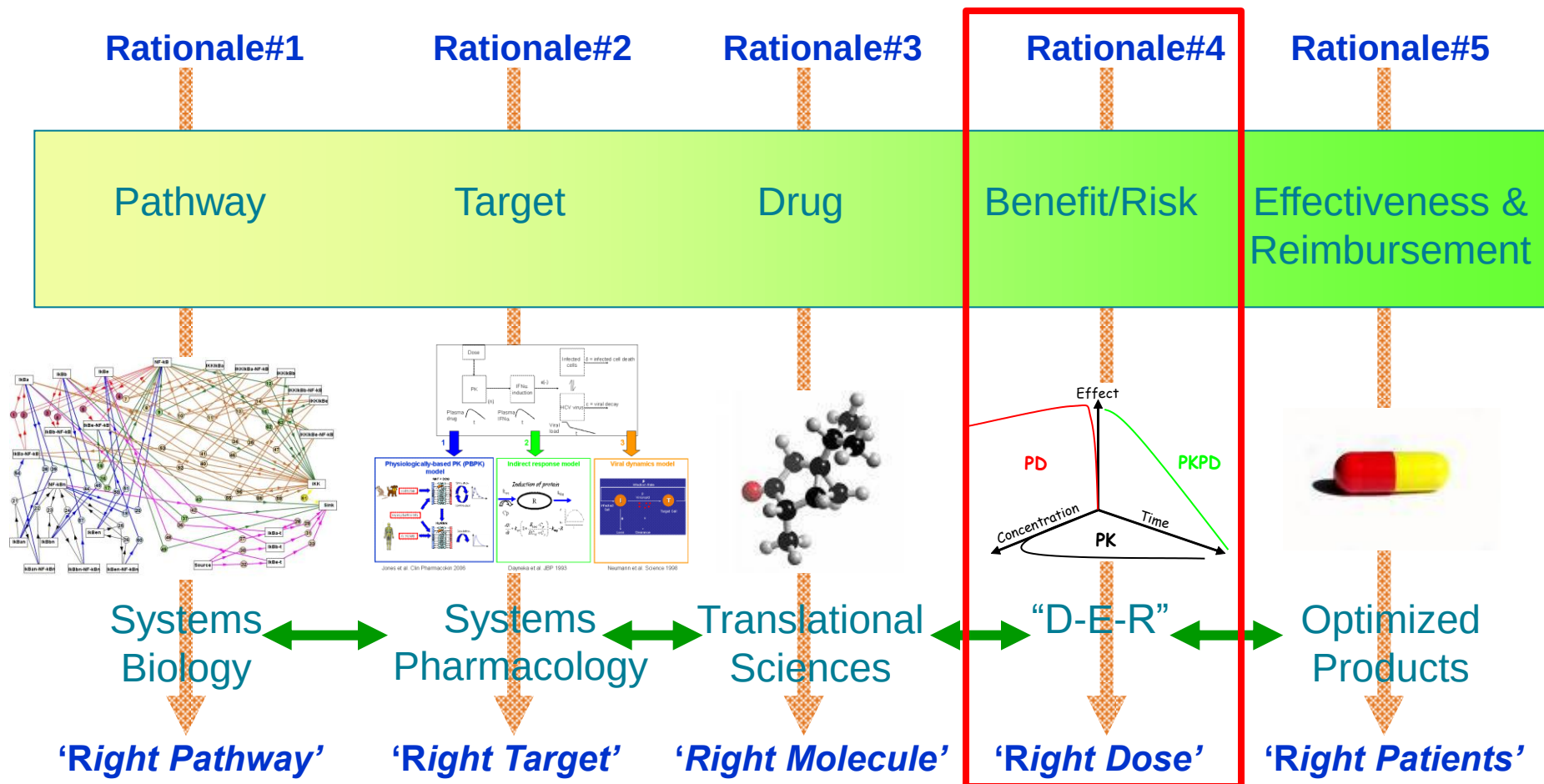


Efficacy is the major problem

Opportunities for Greater Utilization of Quantitative Approaches

- Failure rate in Phase 2 can be attributed to target selection
 - Animal models of disease are often not predictive of efficacy in humans
 - H. Bart van der Worp et al. PLOS Medicine 2010;7:e1000245
- Once target and compound are selected the benefit: risk in humans is largely pre-determined
 - Clinical development serves to uncover the drug's inherent properties sooner or later
- Better understanding of human biology, pathophysiology can be achieved via mechanistic models
 - Increased confidence in drug targets that have evidence of human validation
- Failure rate in Phase 3 can be attributed to inadequate “risk decisions”
- The systematic integration of compound specific (direct) and mechanism and disease area (indirect) relevant information is required in order to create a comprehensive, complete and contemporary body of evidence

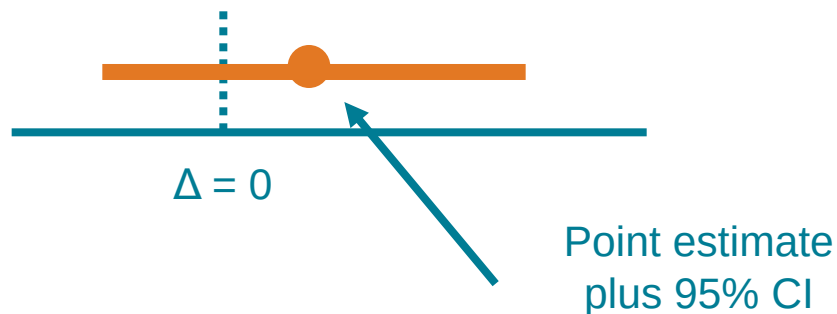
Decision Making: Vertical and Horizontal Challenges for Data/Knowledge Integration



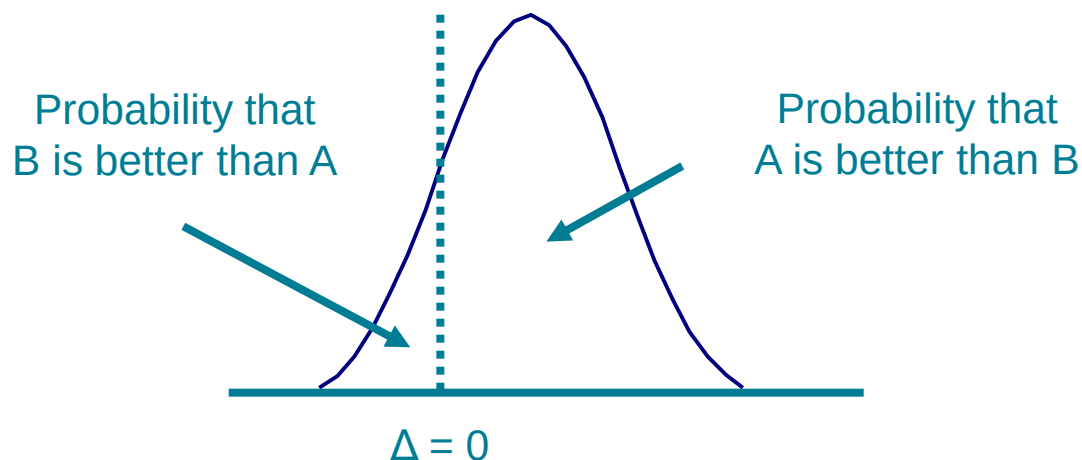
Accumulation of “Evidence” via Meta Analysis

- A quantitative review and synthesis of results from related but independent studies (*Normand, 1999*)
- Aggregate data (AD) meta-analysis
 - Based on summary statistics from each trial
 - Mean response, proportion of responders, hazard ratio
- Individual patient data (IPD) meta-analysis
 - Observed response, time-to-event
- If data are collected longitudinally, either approach can be applied at a single time point or as a longitudinal model
 - IPD is better suited for longitudinal models than AD
- Address uncertainty and heterogeneity of studies, increase statistical power, improve estimates of treatment effect, “new” knowledge & questions

Decision Theoretic “Types”



*No significant difference
Between A and B*



*75% Probability that
A is better than B*

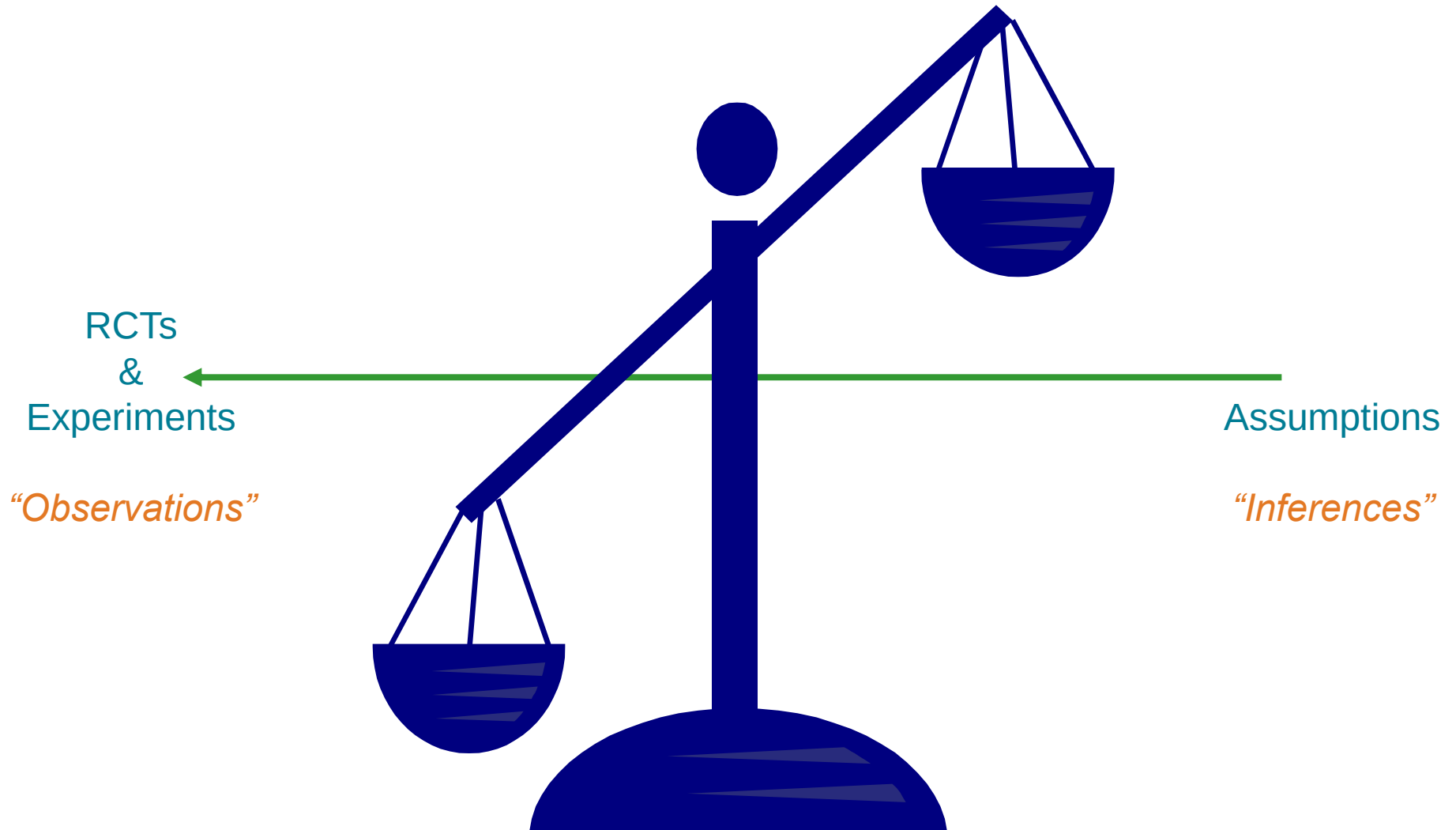
Chuang-Stein C., Kirby S, French JL, Kowalski K, Marshall S, Smith MK, Bycott P, and Beltangady M.
A Quantitative Approach for Making Go/No-go Decisions in Drug Development. *Drug Information J.* 45: 187–202. 2011

“Evidence based medicine is the conscientious explicit, and judicious use of **current best evidence** in **making decisions** about the care of individual patients” taking into account “individual patients predicaments, rights and preferences using **best evidence** from clinically relevant research.”

Sackett et al, 1996

*Acknowledging Deborah Ashby,
Dept of Epidemiology and Public Health, Imperial College London*

Evidence Based Medicine



Viewpoints of Leon Arons to facilitate the Panel Discussion

Viewpoint

Leon Aarons

Model Based Reasoning

- **It's the science, stupid**
- **Classical, hypothesis driven clinical trials ARE scientifically based but are narrow in their perspective and consequently inefficient**
- **A good model summarizes much, but not all, of what is known and so model based reasoning gets to the scientific issues directly**
- **Nevertheless model based reasoning does not obviate the need for GCP and careful trial design**
- **The learn and confirm paradigm is a scientific driven process : modelling is the vehicle for unlocking the science**

Viewpoints of Nick Holford to facilitate the Panel Discussion

The Questions

Why is the concept of the target concentration not guiding drug development during all clinical phases?

And why are regulators not asking for the corresponding dosing target to guide therapy?

Pieter Bruegel il Vecchio

La parabola dei ciechi *(the blind leading the blind)*



Aim and Hit the Target



Target Conc	Dose Model
Initial Peak	Loading Dose = Target Conc x Volume of Distribution
Average Steady State	Maintenance Dose Rate = Target Conc x Clearance

Holford NH. The target concentration approach to clinical drug development. Clin Pharmacokinet 1995; 29: 287-91.

Viewpoints of Peter Milligan to facilitate the Panel Discussion

PAGE Panel Questions

Peter Milligan



Why is the concept of the target concentration not guiding drug development during all clinical phases? And why are regulators not asking for the corresponding dosing target to guide therapy?

- Should indeed “target concentration” ubiquitously guide drug development?
- It’s what “explains” an individual’s PD response that matters most (could be plasma PK, could be biomarker, could be prognostic factor, could be early response....)
- PD response of interest will change over time
- We see issues with “one size fits all” concept wrt to dose strength (not ignoring certain advantages)
- We see “concentration at target” as influential in drug development
- I think “target patient” is the more promising concept.....



How does one rationally select a dose in the absence of having characterised a dose response?

- Don't know about rationality but....
- There is a very long track record of doing it “this way”
- It is familiar to many
- Too many assumptions can be bad for you
- Beauty is in the eyes of the beholder
- Who says we need to select “a dose” anyway (see my response to question 1)



If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?

- Need to get into the domain of evidence based medicine whereby an optimally blended mix of observations (RCTs) and inferences (assumptions) are brought to bear
- Both components can be appropriately scrutinized and qualified as “fit or not fit for purpose” within their context of utilization
- Probably needs some upfront positioning on what “success looks like” for this to be most helpful – consortia, patient groups??



Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?

- Modelling community is not homogenous because individual analysts have exposure to different data sources and have different starting/middle/end points in their analyses/beliefs
- Case specific argumentation may win/lose individual battles, but not the overall campaign, and we often can't generalize for the present and future
- Proposal 1 - Need a community adopted, mathematically characterised "paediatrics" (in the absence of any pathological process) that can predict developmental processes throughout individuals lifespan
- Proposal 2 - Need a community adopted, mathematically characterised "paediatrics" (in the presence of particular pathological process) that can predict disease progression throughout individuals lifespan that are not (narrowly) data driven
- In the absence of the above 2 proposals utilize a "scepticism-scale"
 - EMA EFPIA workshop Break-out session no. 3 (P. BAUER and M. POSCH)



It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and how can EFPIA help?

- No comment from me until we hear EMAs viewpoint

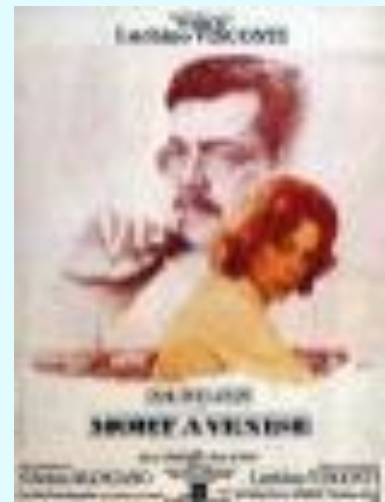


Viewpoints of Gerard Pons to facilitate the Panel Discussion

Panel Discussion

Modelling and Simulation and the Regulatory Process

6th June 2012, 9:00 – 10:15



DISCLAIMER

- **Personal views** expressed here
- **Neither EMA nor PDCO** (PDCO member as external expert)

Gérard Pons

G. Pons' personal tentative answer 1

Q1 *Why is the concept of the target concentration not guiding drug development during all clinical phases? And why are regulators not asking for the corresponding dosing target to guide therapy?*

A1

- Because of the preference for the fastest, cheapest shortcut approaches during drug development.

Regulators should be less conservative and more pro-active in innovative approaches and less inhibited in asking more and novelties to manufacturers.

- Trying to link drug effect(s) to drug exposure instead of dose administered may represent an important progress in evaluation of medicinal products.

G. Pons' personal tentative answer 2

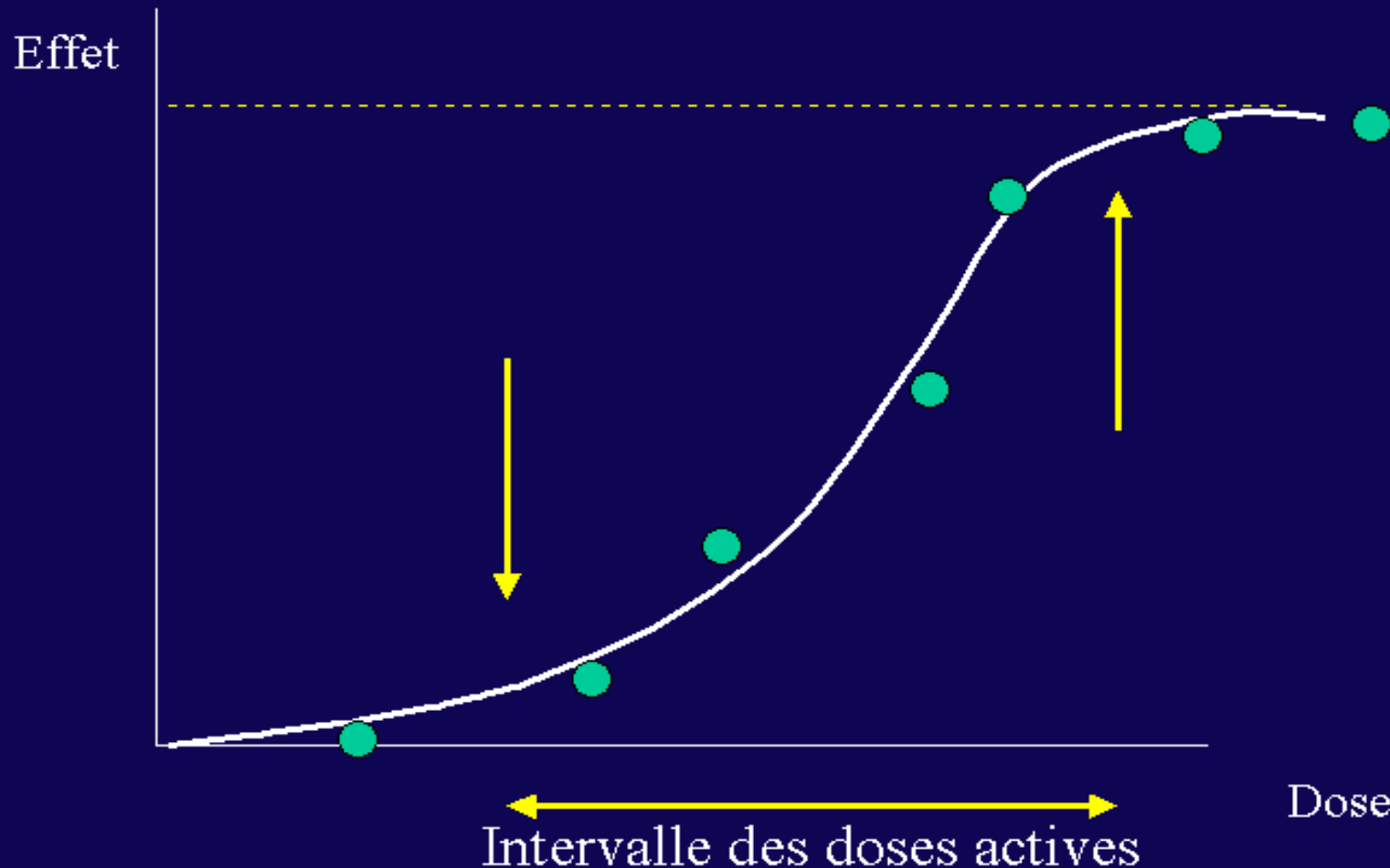
Q2 How does one rationally select a dose in the absence of having characterised a dose response?

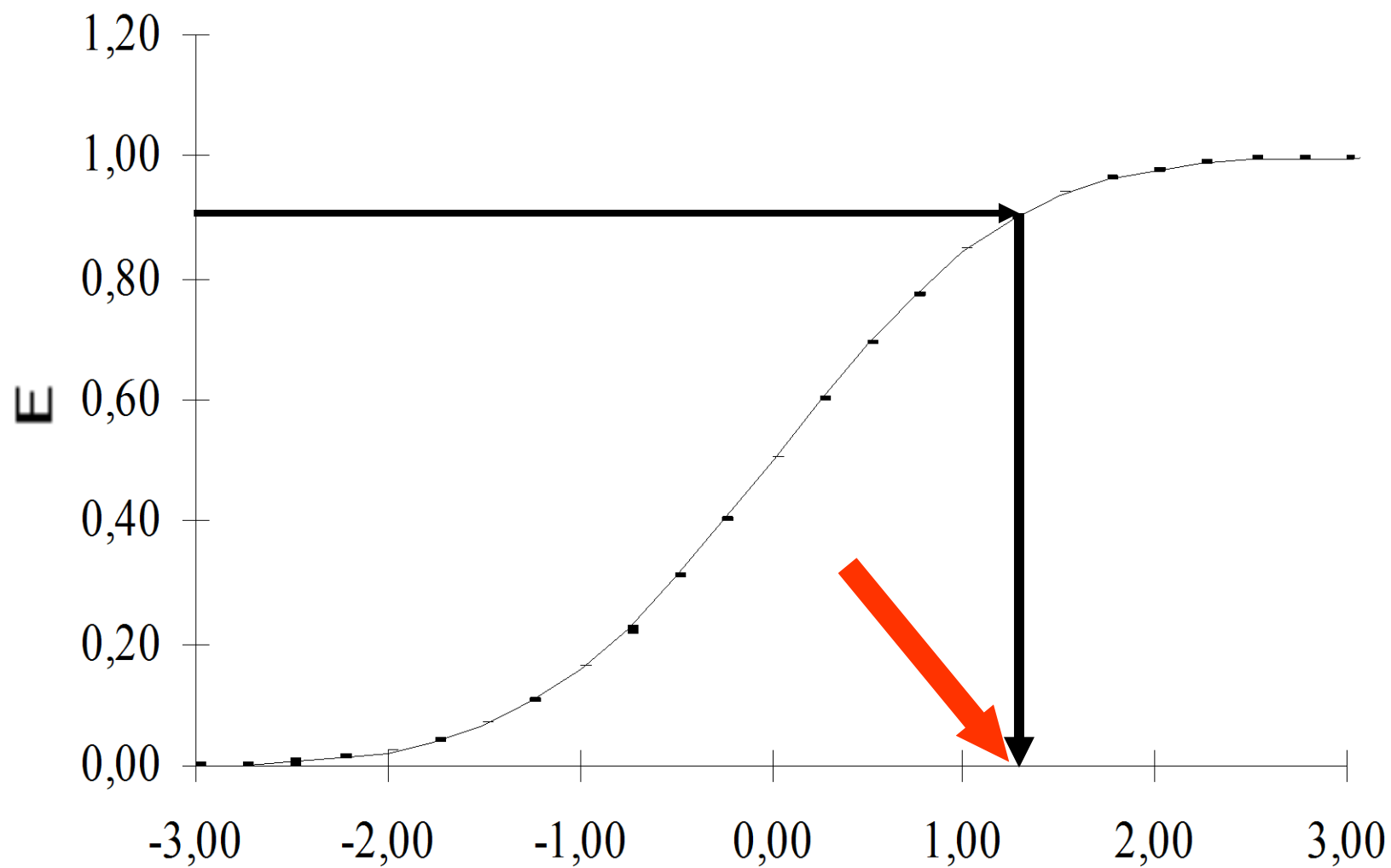
A2 Using dose escalation which is questionable in many instances. Dose-finding studies are often overlooked during drug development. **Innovative methods** should be further introduced into drug development e.g. Bayesian sequential approaches such as the

Continuous Reassessment Method (CRM)

PHASE 2 – OBJECTIVES : DOSE-EFFECT

Relation dose - effet



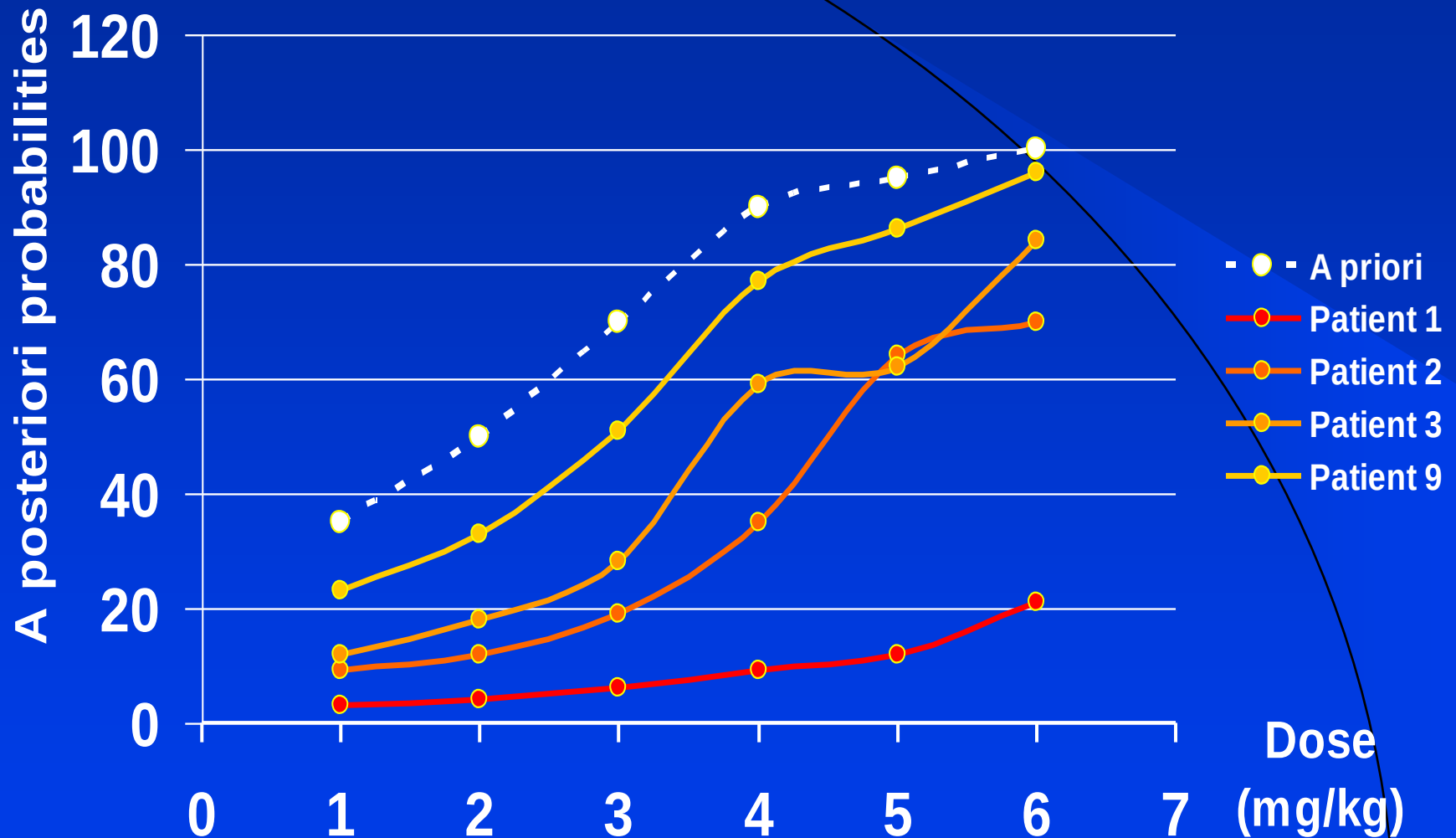


BAYESIAN SEQUENTIAL APPROACH

A posteriori estimated probabilities of success of the six tested doses, updated after each included patient

Subject	Administered dose (n°)	Clinical response	Dose-range studied					
			1	2	3	4	5	6
			A priori probabilities of success (%)					
			35	50	70	90	95	100
			A posteriori estimated probabilities of success (%)					
1	3	Failure	3	4	6	9	12	21
2	6	Success	9	12	19	35	64	70
3	6	Success	12	18	28	59	62	84
9	6	Success	23	33	51	77	86	96
10	5	Success	25	37	56	81	89	97
13	5	Success	31	45	65	87	93	99
14	4	Success	33	47	67	88	94	99

BAYESIAN SEQUENTIAL APPROACH

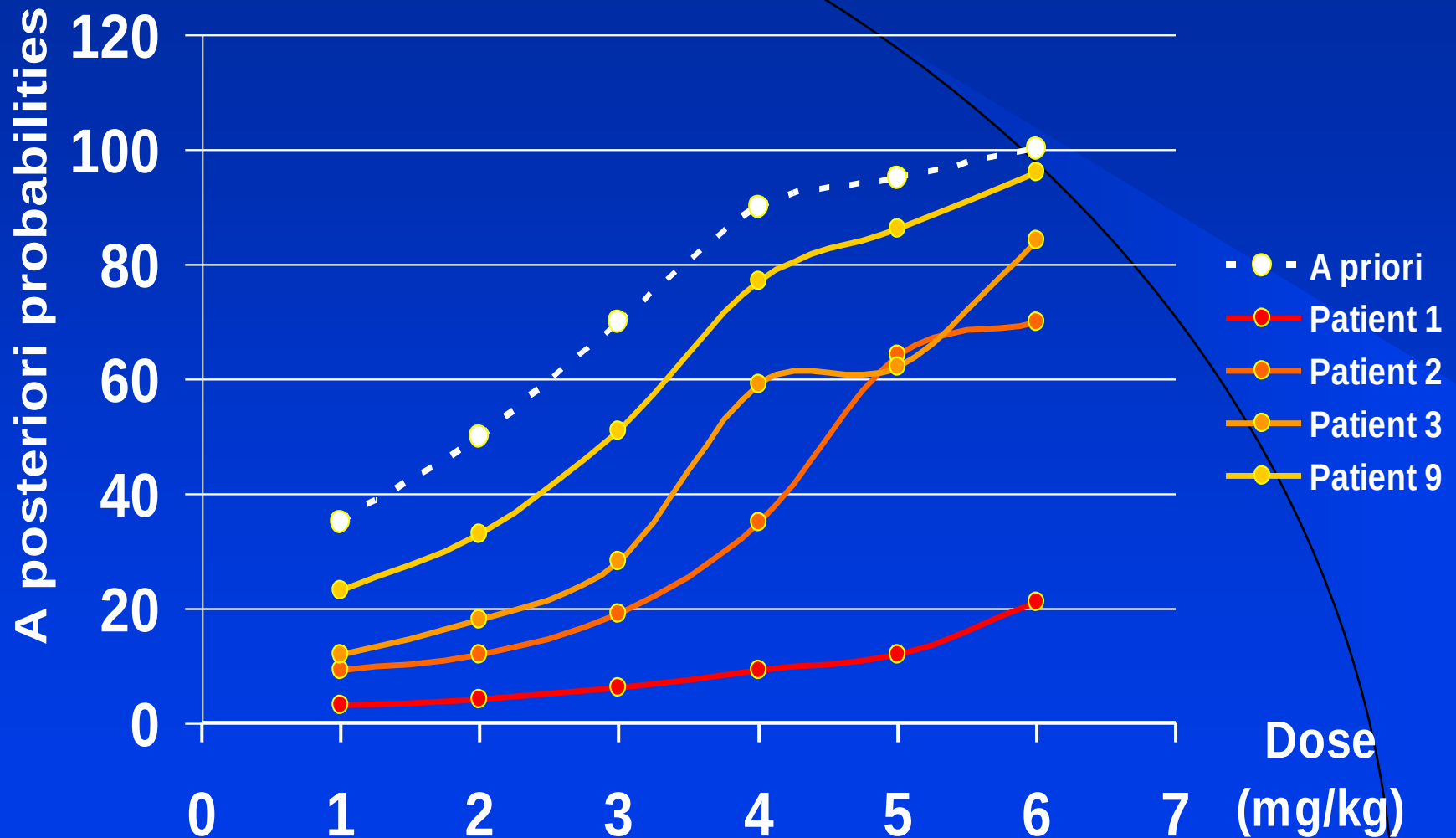


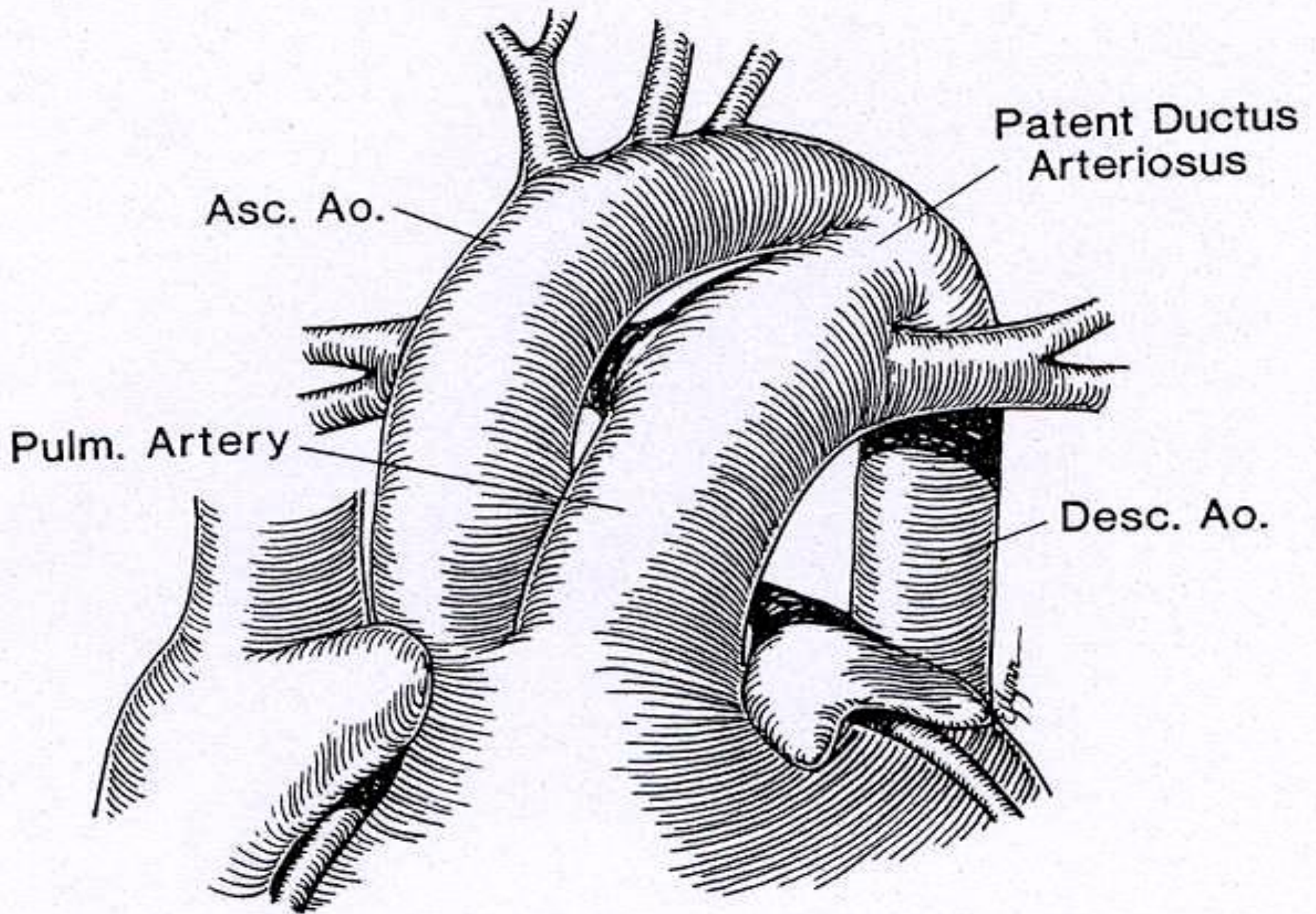
BAYESIAN SEQUENTIAL ANALYSIS

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			A posteriori estimated probabilities of success (%)					
15	4	Success	35	49	69	90	95	99
16	4	Failure	26	38	56	81	89	97
17	5	Success	27	39	58	82	90	98
22	5	Success	31	44	64	87	93	98
23	5	Success	31	45	65	87	93	99
24	4	Success	32	47	67	88	94	99
25	4	Success	33	48	68	89	94	99

BAYESIAN SEQUENTIAL APPROACH





Anatomy of patent ductus arteriosus

BAYESIAN SEQUENTIAL ANALYSIS

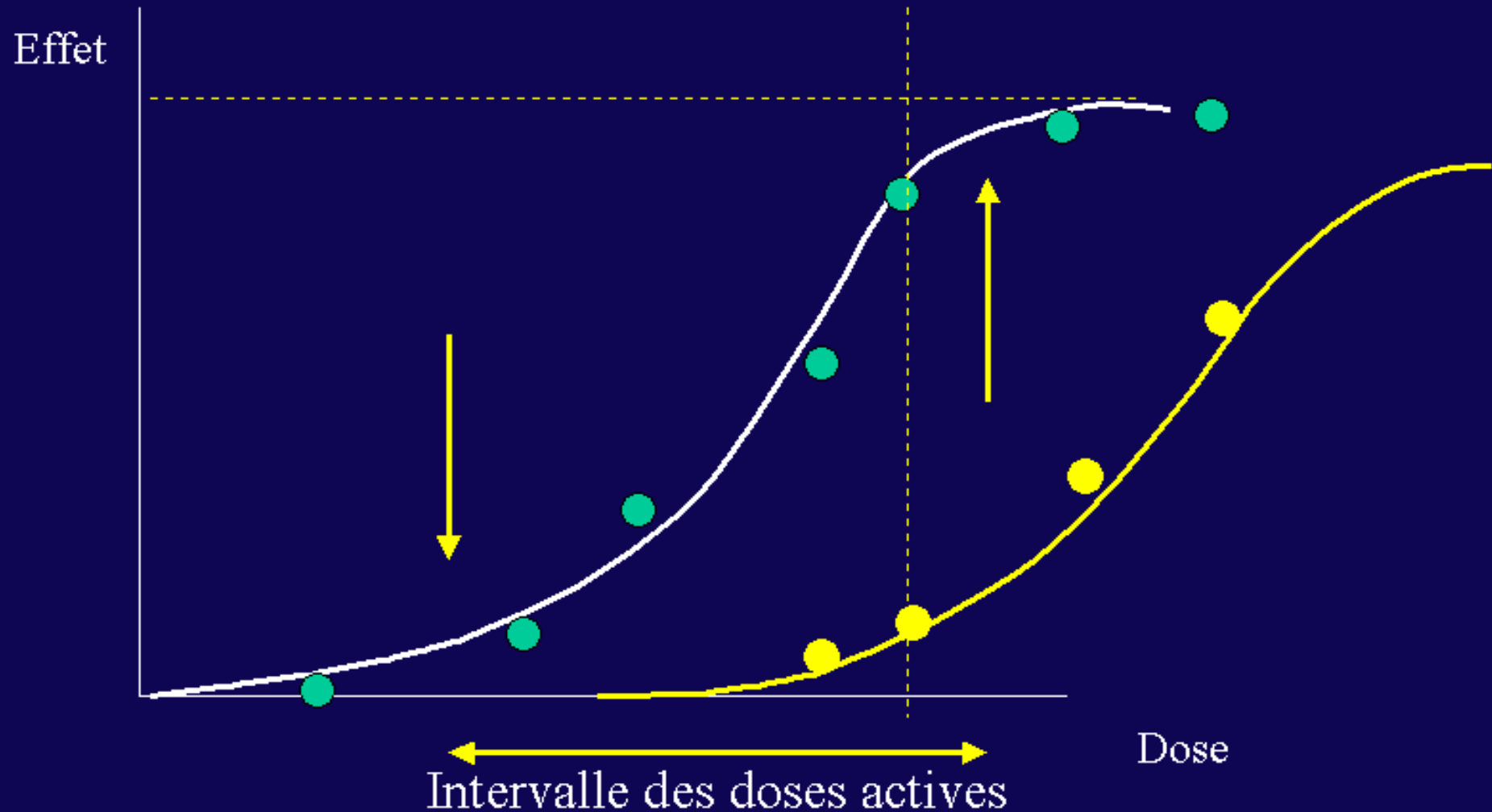
A posteriori estimated probabilities of success

Curative IV NSAID in patent ductus arteriosus

		Dose (mg/kg)			
		5	10	15	20
		<i>A priori</i> estimated probabilities of success (%)			
		0,6	0,8	0,9	0,95
Patients	Dose	<i>A posteriori</i> estimated probabilities of success (%)			
1	10	0,481	0,683	0,812	0,891
2	5	0,370	0,544	0,682	0,787
3	15	0,539	0,744	0,861	0,925
4	10	0,512	0,717	0,840	0,915
5	15	0,467	0,667	0,799	0,882
6	15	0,500	0,703	0,829	0,903
7	10	0,519	0,723	0,845	0,914
8	15	0,553	0,757	0,870	0,931
9	10	0,567	0,771	0,880	0,938

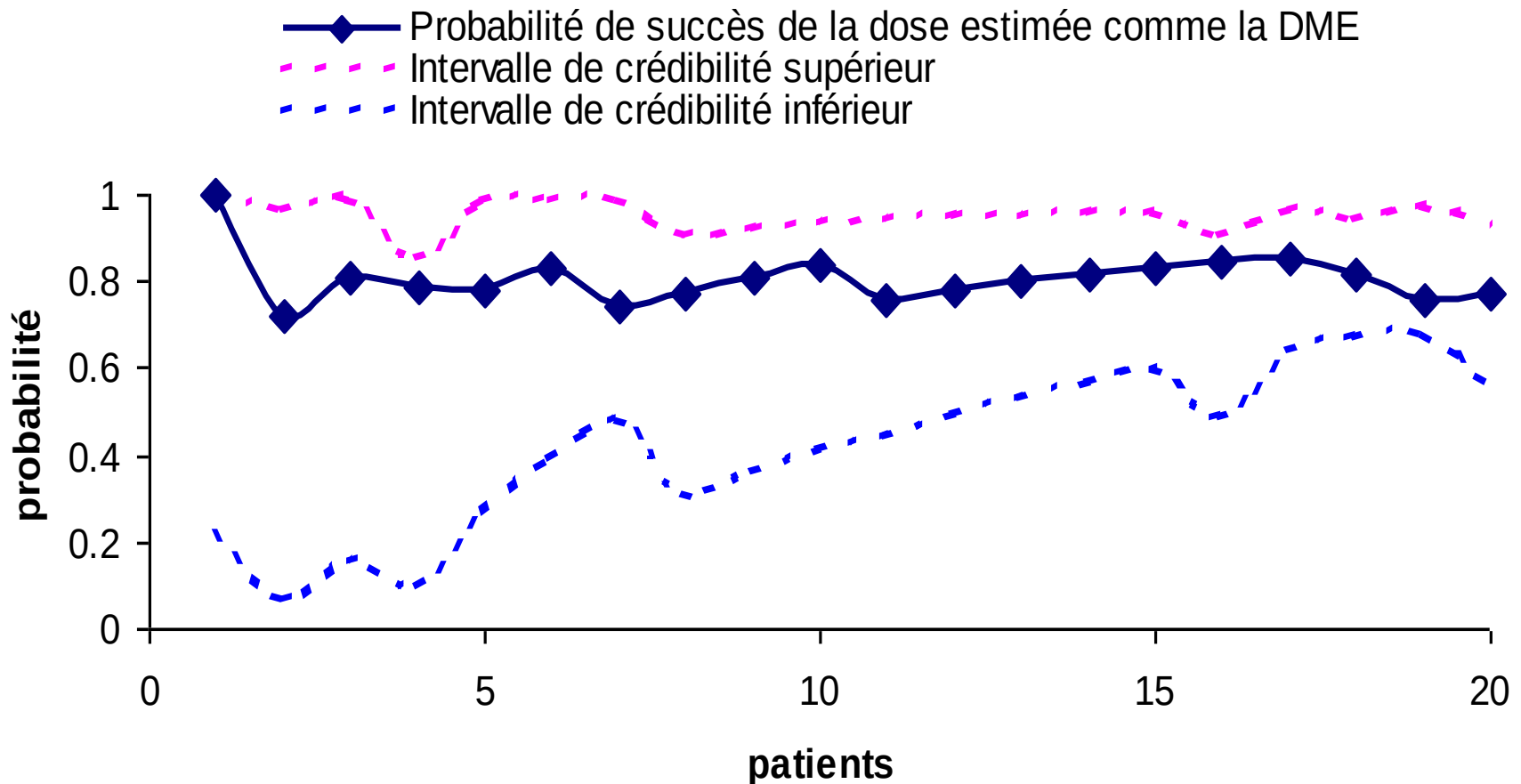
PHASE 2 – OBJECTIVES : DOSE-EFFECT

Relation dose - effet



BAYESIAN SEQUENTIAL ANALYSIS

A posteriori estimated probability of success of the minimal efficient dose (95 % credibility interval)



BAYESIAN SEQUENTIAL ANALYSIS

● ADVANTAGES

- NO PLACEBO GROUP REQUIRED**
- ETHICS**
- LIMITED NUMBER OF PATIENTS**

● FLAWS

- QUALITATIVE PARAMETER**
- RAPID EVALUATION OF RESPONSE**
- ORGANIZATION**

G. Pons' personal tentative answer 3

Q3 *If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?*

A3 - Emphasis should be given on the

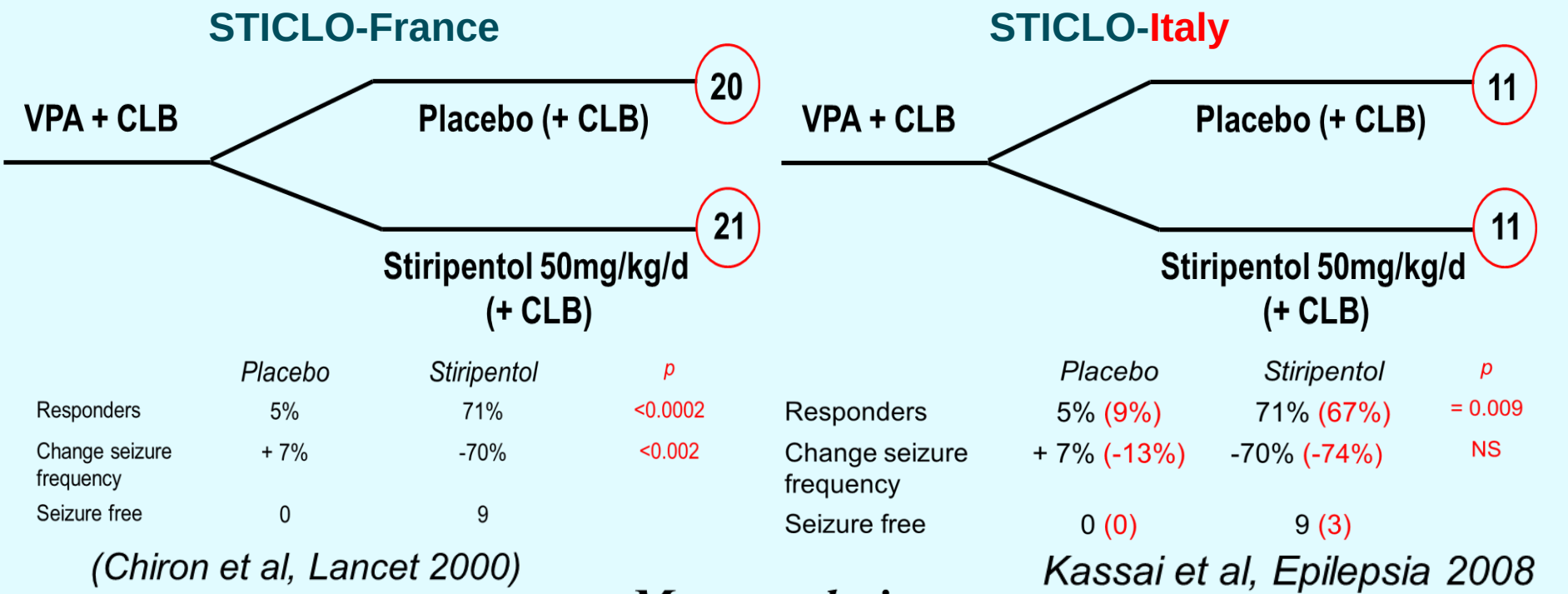
magnitude of the treatment-effect

and the religion of the p-value replaced by the simple expression of “significant” versus “non significant” (approach that can infer to guide the approval to a new medication.

Ex.: stiripentol in Dravet syndrome (SMEI)

G. Pons' personal tentative answer 3 (... continued)

RCT on STP-CLB combinaton in DRAVET syndrome (SMEI)



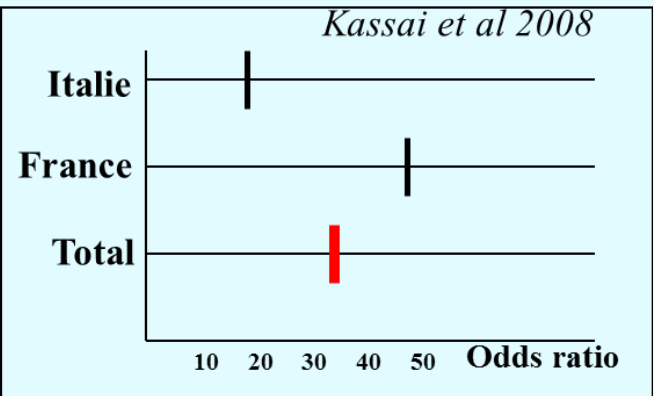
Meta-analysis

STP in SMEI

Chiron et al 2000

41 (France)

22 (Italie)



G. Pons' personal tentative answer 4

Q4 Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?

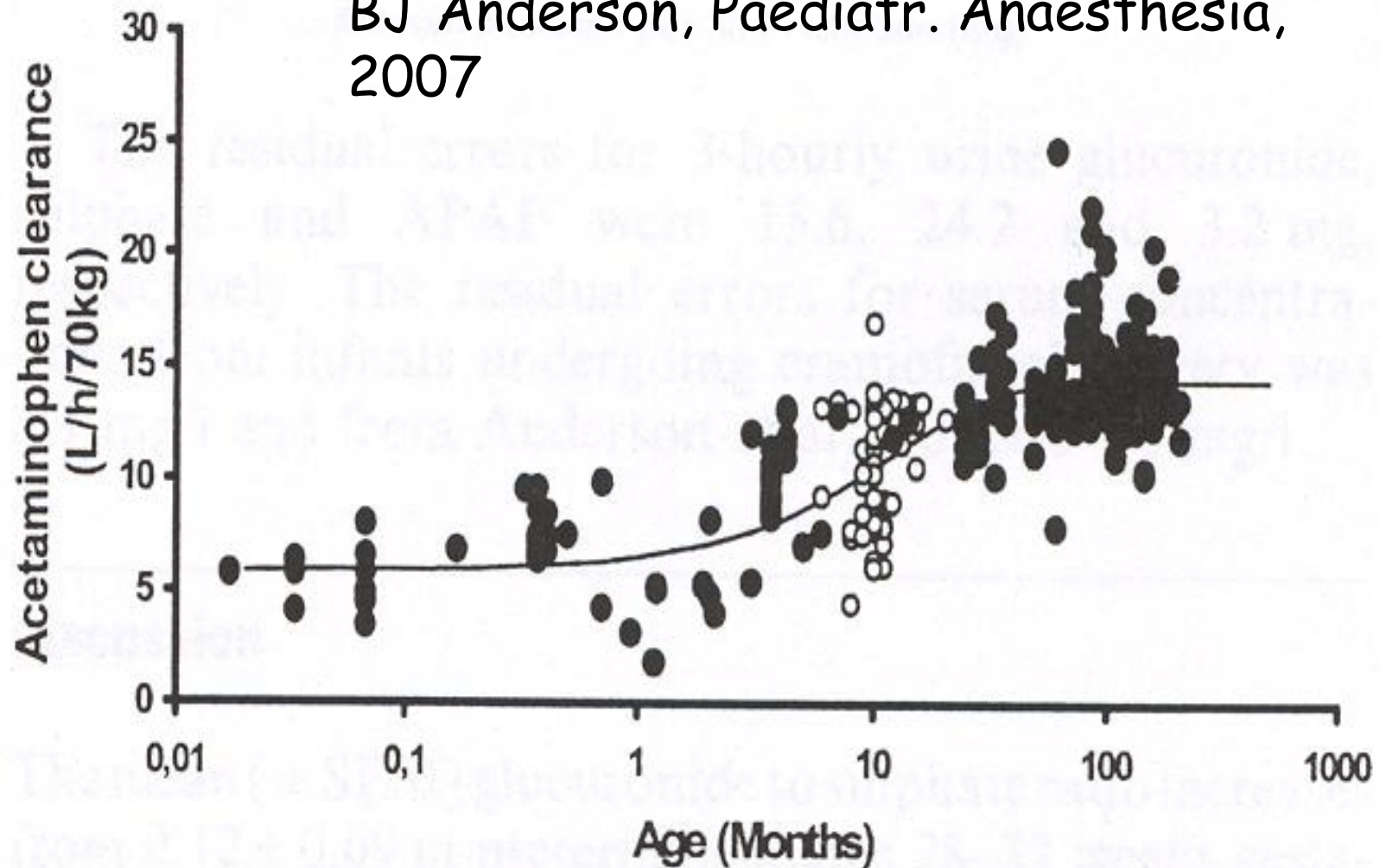
A4

A systematic **validation of the model** should be provided by the drug developer using additional sparse data collected in an observational real-life post-marketing setting and the model amended accordingly if the new data do not properly fit the proposed model (e.g. **physiology-based modelling**).

New data should be generated in a descriptive manner during drug development e.g. on the **maturational profile** of PK (e.g. clearance, specific functions of elimination) and PD (or PK/PD) parameters, and modeled as a function of age, made publically available (EMA web site) for future paediatric use.

MODELLING OF MATURATION & SIMULATION

BJ Anderson, Paediatr. Anaesthesia,
2007



G. Pons' personal tentative answer 4

Q4 Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?

A4

Manufacturers should be **more scientifically proactive** in such a way that regulators will have no other choice than to adjust and update the already existing guidelines for these to meet the current level of scientific knowledge, the current state of the art.

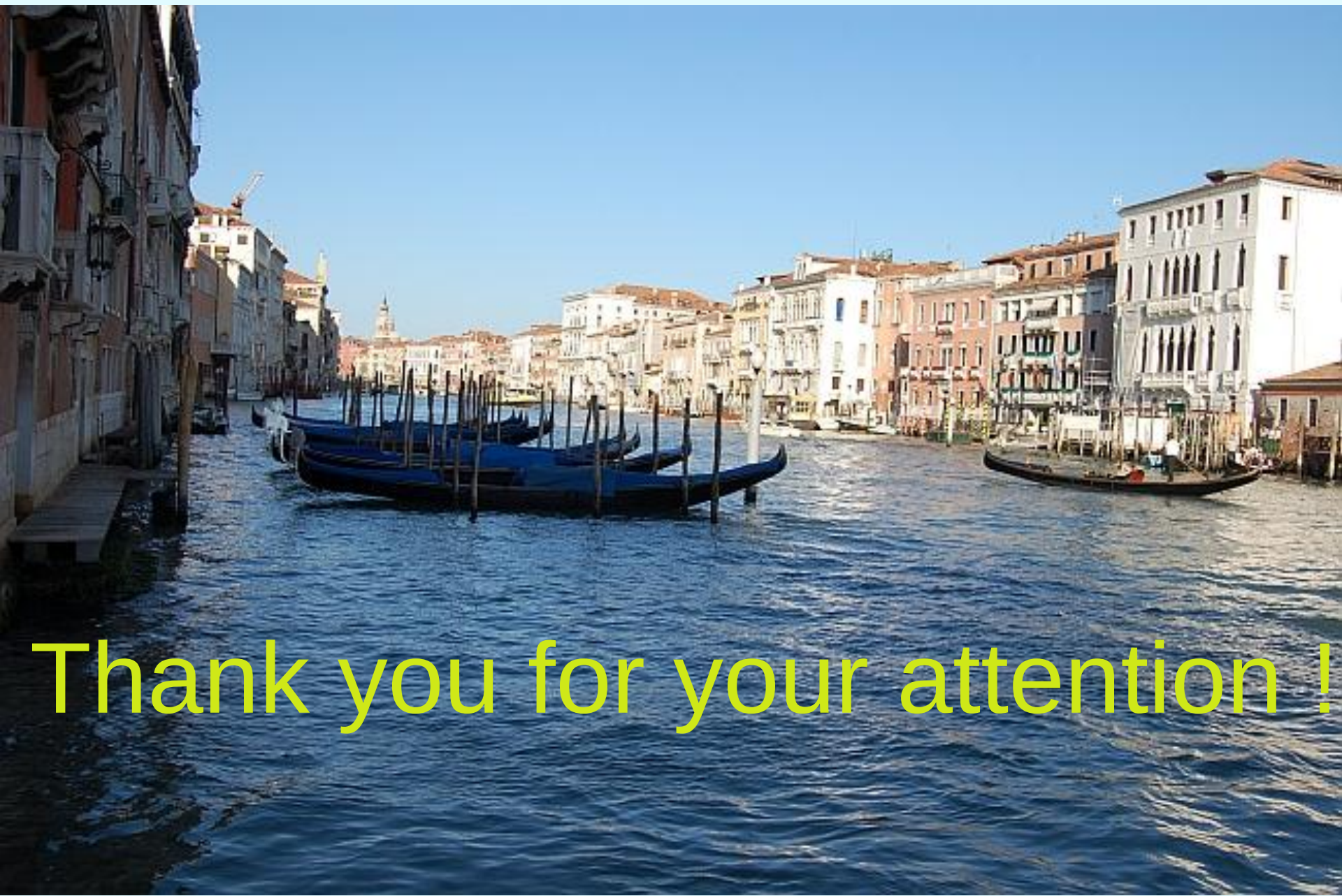
Manufacturers have a tremendous **potential force of scientific proposal** and should use it.

The questions to be discussed 5

Q5 *It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and how can EFPIA help?*

A5

Only **EMA representatives** can eventually answer this question.



Thank you for your attention !

Viewpoints of Mick Looby to facilitate the Panel Discussion

Dose Response in the Real World

Indacaterol: Traditional vs Model Based Approaches

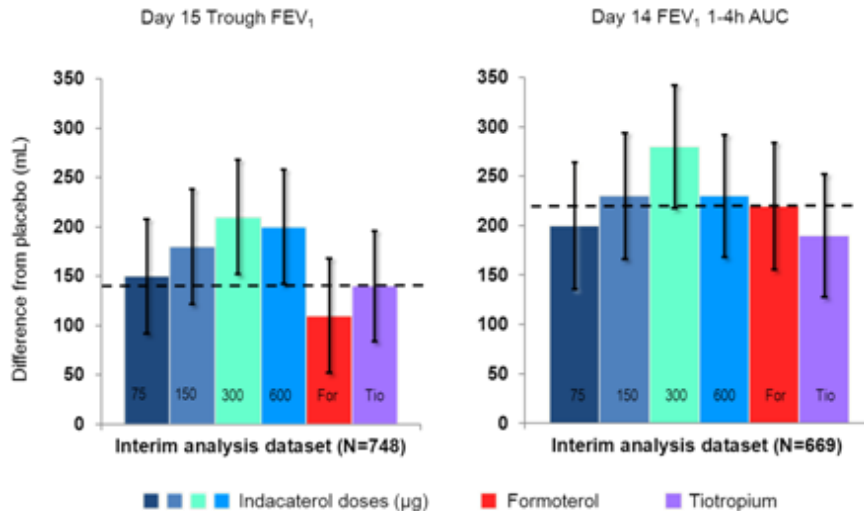
Michael Looby & Didier Renard

The traditional approach

- The traditional ANCOVA approach to dose ranging compares active doses and placebo (contrast statistics) to determine the existence of a dose response and, if so, to select a target dose. If the difference between placebo and at least one of the doses is statistically significant, the presence of a dose-response relationship has been confirmed: i.e. there is a positive treatment effect. The target dose is then estimated as the smallest statistically significant dose which has an average effect that is clinically relevant according to a pre-specified value of clinical relevance (J Biopharm Stat. 17, 6, 965-95)
- The traditional approach is designed to detect, but not characterize a dose response
- It is not unusual that low signal to noise means statistically differentiating active doses not possible, though differentiating from placebo is possible
- The FDA Guidance
 - In principle, being able to detect a statistically significant difference in pair-wise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established using all the data.

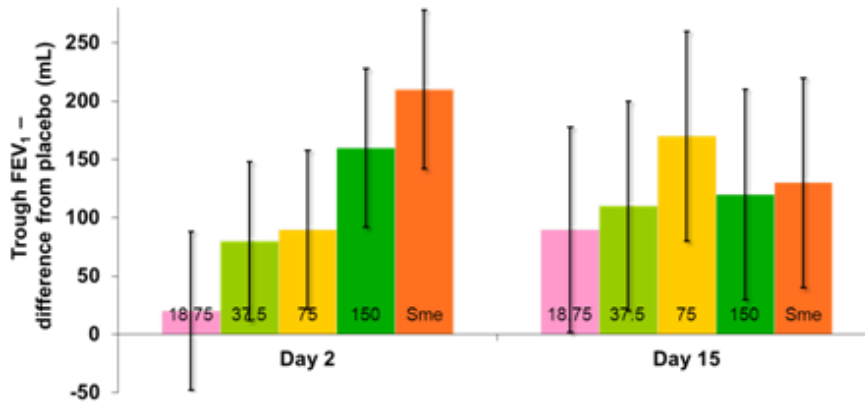
Original dose selection trial

- Lowest doses that exceed comparators. Agreed with all regulators
- Numerical comparison selected 150 & 300 mcg
- This was the basis of the approval round the world
- FDA insist further dose ranging necessary

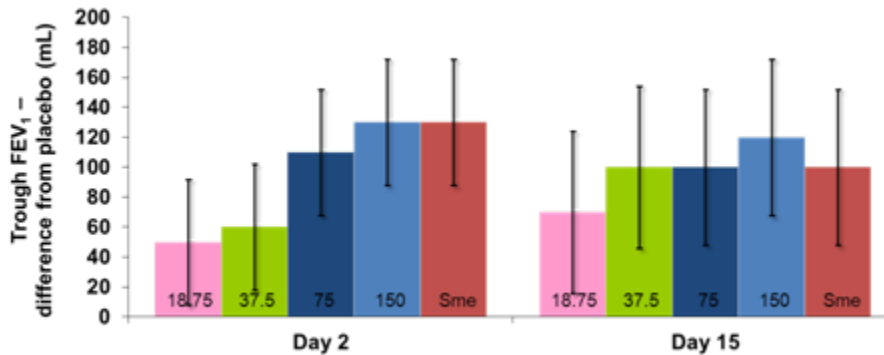


Indacaterol: traditional dose ranging trials

Asthma



COPD

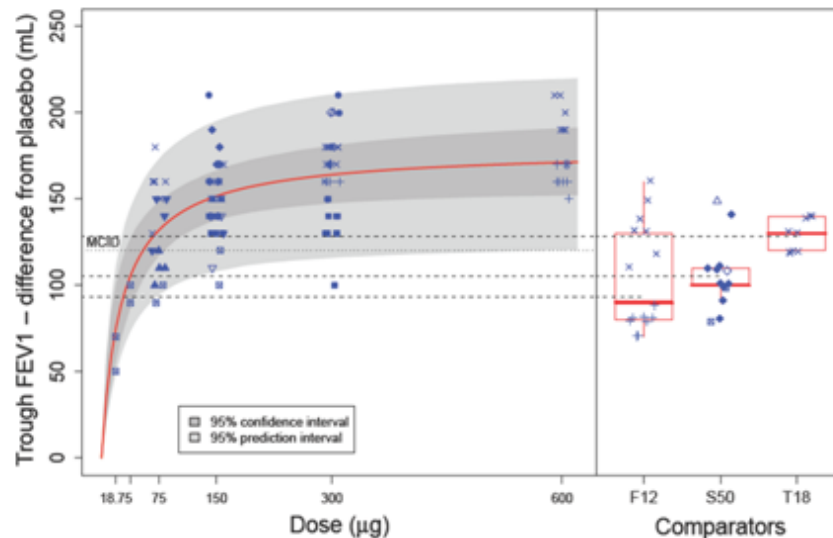


- “there was some increase in efficacy with larger doses, with the results with the 75-µg and 150-µg doses separating from those achieved with lower doses; however, at week 2, the effects of different doses were harder to discriminate from one another, which suggests that the bronchodilator effect of indacaterol had reached a plateau. Given the variability of FEV1 response, the effect in some patients who receive a 37.5-µg dose may still lie on the upward slope of the bronchodilator-effect curve, whereas with the 75-µg dose, the effect in most patients will be on the plateau.”

- The FDA’s Review, New England Journal of Medicine. Vol 365, 24, 2247-2249

Indacaterol: model based approach

Bayesian meta-analysis of dose response in COPD

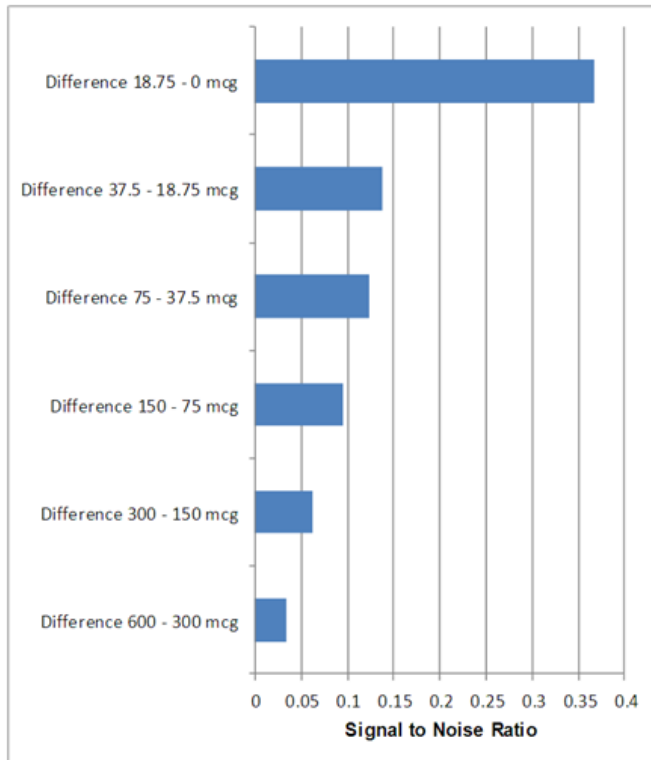


Respiratory Research 2011, **12**:54

- **Our conclusions (*Respiratory Research*. 12, 54)**
 - There is a 92 % probability that 37.5 µg is less than the MCID of 120 mL.
 - There is a 95 % probability that 75 µg exceeds the MCID.
 - 150 µg has an incremental benefit over 75 µg and is the lowest indacaterol dose that exceeds the average bronchodilation observed for the comparators.
 - 150 µg is located mid-way between the MCID and the maximum response and exceeds all comparators.
 - 300 µg intersects the maximum response.
- **FDA conclusion (*International Journal of Clinical Pharmacology and Therapeutics* – in press)**
 - The assumed Emax model is not supported by the study level data and the study level analysis over estimates the incremental difference between two adjacent doses
 - We predict 20 mL between 75 and 150 mcg
 - FDA says it is 0 mL
- **Our Reply (*International Journal of Clinical Pharmacology and Therapeutics* – in press)**
 - No alternative quantitative approach presented.
 - FDA assessment of model based approach lacks precision to falsify it.

Concluding thoughts

Bronchodilators: low signal to noise



Visualizing dose-response when the signal to noise ratio is low: the bronchodilatory response in COPD

A Picture is Worth a Thousand Tables: Graphics in Life Sciences.

Edited by Andreas Krause and Michael O'Connell. Published by Springer-Verlag / AAPS in 2012 (in press)

- Sometimes model based approaches are the only reasonable option
- Low SNR means that the traditional approach may not meaningfully differentiate active doses in reasonably sized trials
 - Often traditional approach is so inefficient that rational dose selection is impossible
- Low SNR means that *potential* bias associated with model based approach pales into insignificance compared to imprecision of traditional approach
- Spelling out such difficulties in well written guidance documents would help break the vicious cycle of “uninformed expectations” that exists between industry and regulators

Viewpoints of Terry Shepard to facilitate the Panel Discussion

Q1: Why is the concept of the target concentration not guiding drug development during all clinical phases? **And why are regulators not asking for the corresponding dosing target to guide therapy?**

- Consensus – unclear/inadequate exploration of dose-response (efficacy and safety) and justification of dose selection in many submissions – too much risk entering phase III
- A well characterised dose response (clinical endpoint or validated surrogate) is always viewed as highly desirable by regulators, however ...
- Benefit:risk decisions – mandate to focus on outcomes and uncertainties
- Regulatory guidance aims to ensure an adequate evidence base for regulatory decision, not to tell companies how to develop drugs – expect change to primarily come from within; however, see also question #5.
- Scientific advice - encourage companies to better understand these relationships (philosophy: companies and regulators share risk of inappropriate dose selection)

Benefit Risk Decisions EMA Framework

Beneficial effects	Uncertainty of beneficial effects
Unfavourable effects	Uncertainty of unfavourable effects

Overall and in important subgroups,
under experimental conditions
reflecting clinical practice

Validity of extrapolation, surrogacy, variability, important sources of bias, methodological flaws or deficiencies, limitations of the data set (sample size, duration of follow-up), unsettled issues.

**Mitigation of
supportive
nonclinical and
clinical data**



Q3: If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?

- Viewed as where the tool of M&S potentially brings greatest public health value
- Recognise as “pole vault” (i.e. highest level of regulatory scrutiny → highest level of encouragement for scientific advice, expectation regarding documentation)
- Concept paper: surrogate endpoints, borrow information from other drugs (see paper when released for consultation)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 April 2012
EMA/918316/2011

PDCCO

Concept paper on extrapolation of efficacy and safety in
medicine development.

Q4: Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. **What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions?** Should we just wait for new guidances?

- Understand regulatory questions and issues

Benefit:risk decisions (EPARs), M&S to ensure safe and effective drugs in older people*

- Engage regulators on M&S

Ask for scientific advice – include extensive documentation, discussion of **assumptions**, **biological plausibility**, etc – provides experience to assessors at a time when not critical to benefit:risk decision – opportunity for mutual learning – pharmacometricians, clinical pharmacologists should **attend scientific advice meetings**

- Put equal effort into effective communication

Clinicians (+ clinical pharmacologists) + statisticians + pharmacokinetics assessors + (preclinical/quality assessors) **must be convinced** → prerequisites = technical quality, but also clearly communicated and contextualised in language of relevant experts

Ted Grasela and heuristics, engaging project teams to improve communication around models for MBDD
Servier R&D example: “PPP” = People Prefer Pictures

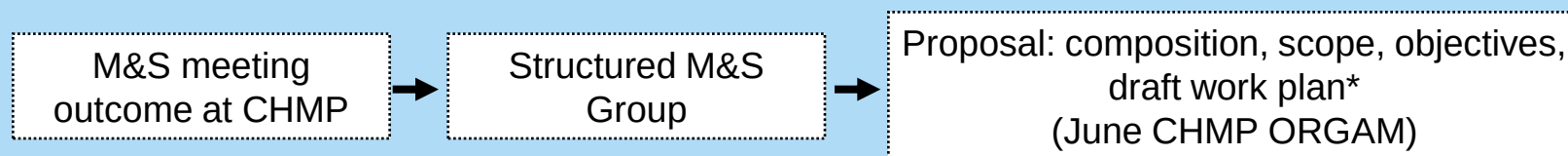
Propofol ADME, PK/PD in Conrad Murray trial – Professor Steven Shafer (Stanford)
(implications of multiexponential disposition; simulations linking dose + method of administration to toxicology results)

Q5: It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. **What are EMA's concrete plans** and how can EFPIA help?

- EMA/EFPIA Workshop on M&S → concrete plans for EMA and CHMP
Currently in proposal stage

- Involvement of key regulators

Rob Hemmings (SAWP chair, CHMP member, MHRA), Tomas Salmonson (CHMP vice Chair, MPA)



- Current thinking (i.e. not agreed, not prioritised, not promised, but current wishes)

A key objective: to enhance the collective competence and capacity to provide scientific advice and assessment of M&S in MAAs

Possible areas for regulatory guidance / reflections: Update of approach to dose finding, reflection paper on M&S, guidance (Q&A) on how best to incorporate M&S in eCTD structure, reflection paper on use of M&S in support of FIM, guideline on extrapolation (with extrapolation working group), update to guideline on reporting results of population PK analyses (with PKWP)

Training envisaged: regular programme of assessor training as guidelines are developed, follow up workshops on specific topics (e.g. dose finding)

Collaborations envisaged: Scientific Advice Working Party, Biostatistics Working Party, Pharmacokinetics Working Party, Paediatric Committee (+ Extrapolation Working Group)

Q5: It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and **how can EFPIA help?**

- Organised feedback

Arrange organised feedback to concept papers, reflection papers, guidelines, etc (e.g. EFSPi, PSI for guidelines from Biostatistics Working Party)

Interesting example of engagement: mock scientific advice at PSI conference (<http://www.psiweb.org/>)



- Continue excellent collaboration with EMA

We've made a good start! As structured M&S group is established, there will be further opportunities to collaborate.

Request from Industrial PBPK Working Group

- Current thinking (i.e. not agreed, not prioritised, not promised, but current wishes)

A key objective: to enhance the collective competence and capacity to provide scientific advice and assessment of M&S in MAAs

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