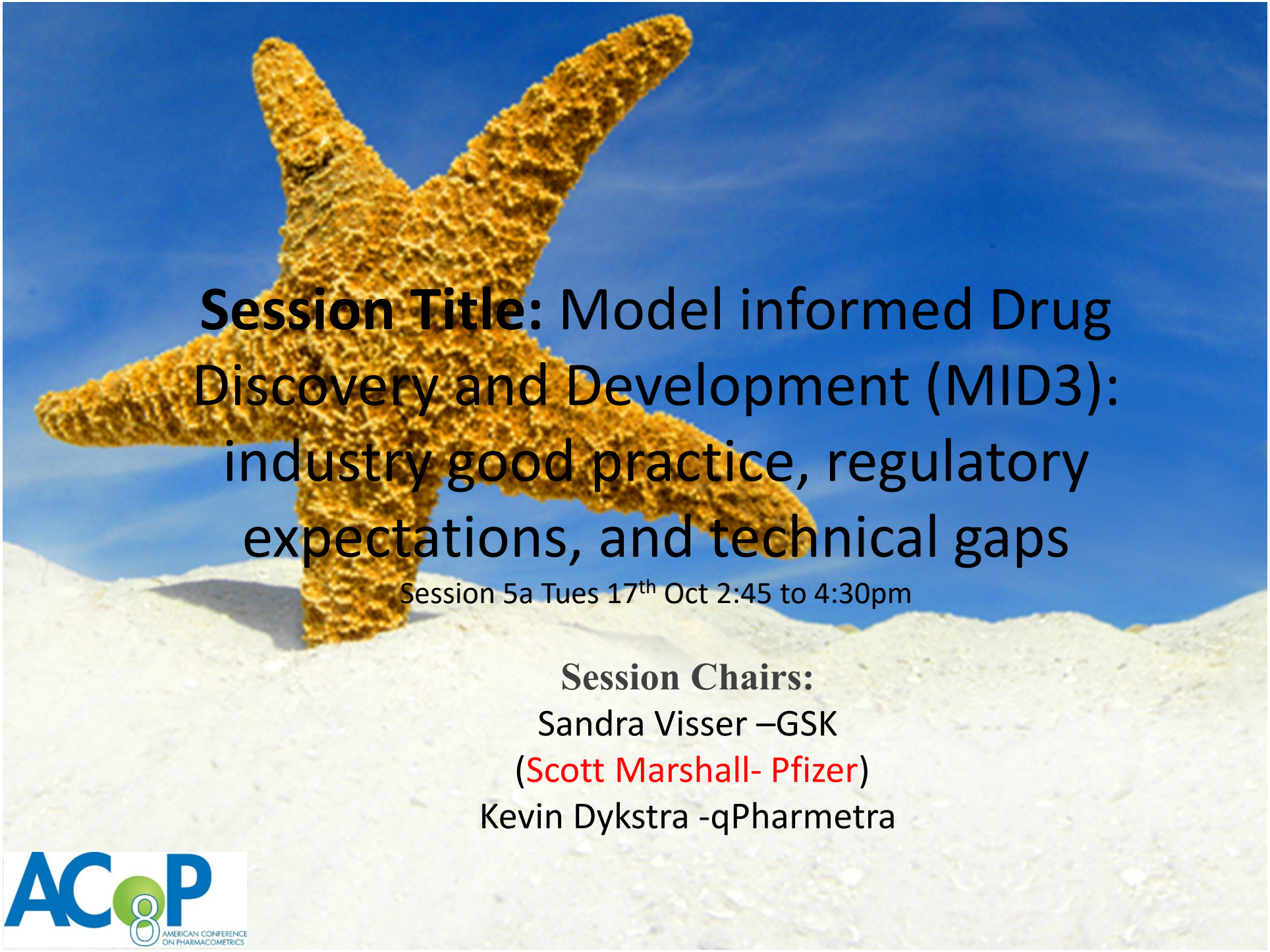


Session Title: Model informed Drug Discovery and Development (MID3): industry good practice, regulatory expectations, and technical gaps

Session 5a Tues 17th Oct 2:45 to 4:30pm

Session Chairs:

Sandra Visser –GSK

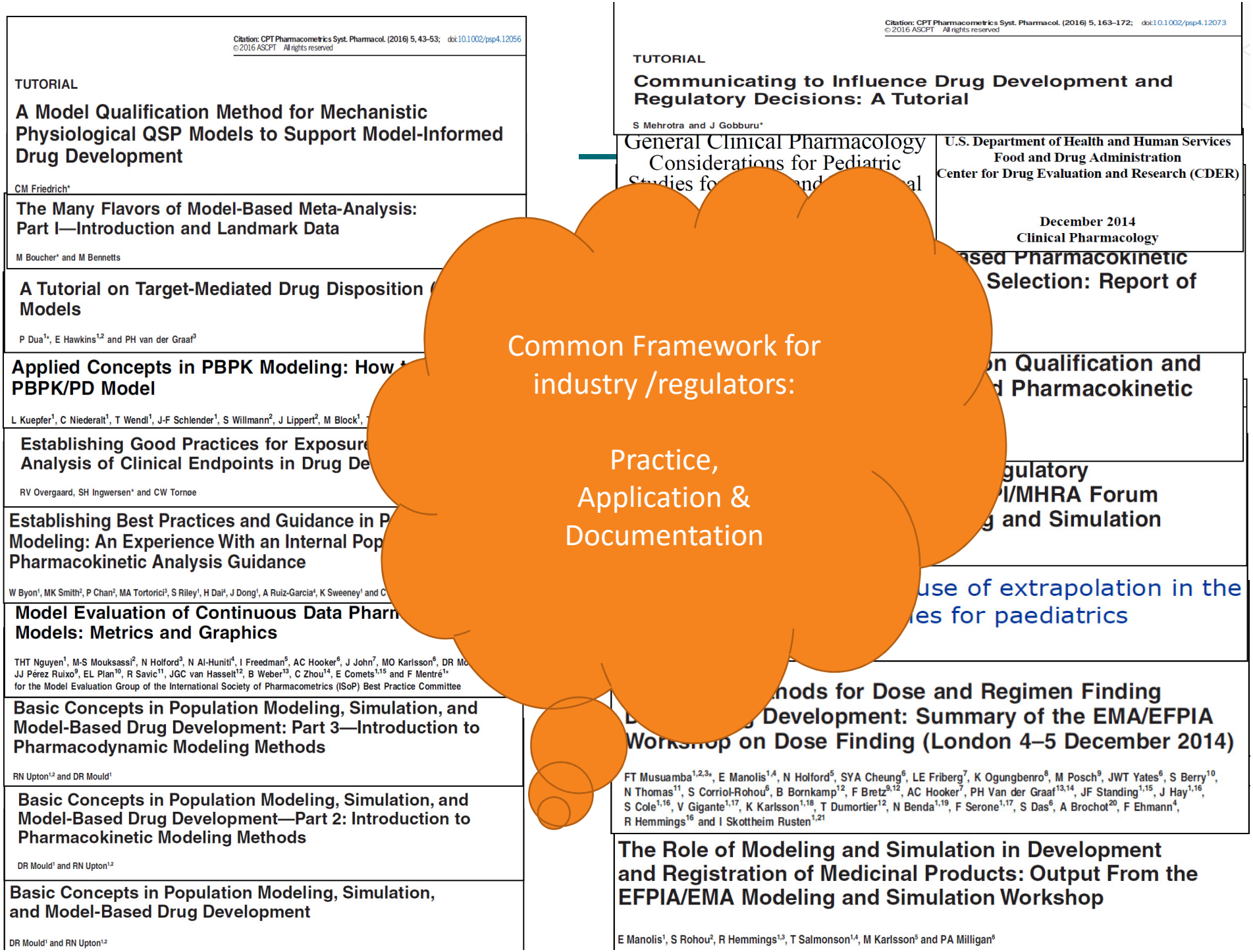
(Scott Marshall- Pfizer)

Kevin Dykstra -qPharmetra

ACoP 8 AMERICAN CONFERENCE ON PHARMACOMETRICS

Outline

- **Overview of MID3 Good Practice Guidelines: Current status in industry & challenges**
  - Dr Scott Marshall (Pfizer Ltd)
- **Do emerging good practice documents (e.g. MID3, model evaluation, pop pK etc) resonate. Gaps and opportunities ?**
  - EMA perspective: Survey Responses
  - Dr Efthymios Manolis (EMA) - Kevin Dykstra (qPharmetra)
  - Guidelines and Good Practices for Advancing Model Informed Drug Development: Gaps and Opportunities
  - Dr Raj Madabushi (FDA)
- **Panel discussion**
  - Speakers and Drs Alexander Staab (*Boehringer-Ingelheim)* , Dr Kevin Krudys (FDA)
  - Facilitator – Kevin Dykstra (qPharmetra)



Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 43–53; doi:10.1002/psp4.12056
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TUTORIAL

A Model Qualification Method for Mechanistic Physiological QSP Models to Support Model-Informed Drug Development

CM Friedrich*

The Many Flavors of Model-Based Meta-Analysis: Part I—Introduction and Landmark Data

M Boucher* and M Bennetts

A Tutorial on Target-Mediated Drug Disposition (Models

P Dua[1*], E Hawkins[1,2] and PH van der Graaf[3]

Applied Concepts in PBPK Modeling: How t PBPK/PD Model

L Kuepfer[1], C Niederalt[1], T Wendl[1], J-F Schlender[1], S Willmann[2], J Lippert[2], M Block[1], T

Establishing Good Practices for Exposure Analysis of Clinical Endpoints in Drug De

RV Overgaard, SH Ingwersen* and CW Tornoe

Establishing Best Practices and Guidance in P Modeling: An Experience With an Internal Pop Pharmacokinetic Analysis Guidance

W Byon[1], MK Smith[2], P Chan[2], MA Tortorici[3], S Riley[1], H Dai[4], J Dong[1], A Ruiz-Garcia[4], K Sweeney[1] and C

Model Evaluation of Continuous Data Pharn Models: Metrics and Graphics

THT Nguyen[1], M-S Mouksassi[2], N Holford[3], N Al-Huniti[4], I Freedman[5], AC Hooker[6], J John[7], MO Karlsson[6], DR Mo JJ Pérez Ruixo[9], EL Plan[10], R Savic[11], JGC van Hasselt[12], B Weber[13], C Zhou[14], E Comets[1,15] and F Mentré[1*] for the Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Best Practice Committee

Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3—Introduction to Pharmacodynamic Modeling Methods

RN Upton[1,2] and DR Mould[1]

Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods

DR Mould[1] and RN Upton[1,2]

Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development

DR Mould[1] and RN Upton[1,2]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 163–172; doi:10.1002/psp4.12073
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TUTORIAL

Communicating to Influence Drug Development and Regulatory Decisions: A Tutorial

S Mehrotra and J Gobburu*

General Clinical Pharmacology Considerations for Pediatric Studies fo and al

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology

sed Pharmacokinetic Selection: Report of

n Qualification and d Pharmacokinetic

gulatory I/MHRA Forum g and Simulation

use of extrapolation in the es for paediatrics

hods for Dose and Regimen Finding Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)

FT Musuamba[1,2,3*], E Manolis[1,4], N Holford[5], SYA Cheung[6], LE Friberg[7], K Ogungbenro[8], M Posch[9], JWT Yates[6], S Berry[10], N Thomas[11], S Corriol-Rohou[6], B Bornkamp[12], F Bretz[9,12], AC Hooker[7], PH Van der Graaf[13,14], JF Standing[1,15], J Hay[1,16], S Cole[1,16], V Gigante[1,17], K Karlsson[1,18], T Dumortier[12], N Benda[1,19], F Serone[1,17], S Das[6], A Brochot[20], F Ehmann[4], R Hemmings[16] and I Skottheim Rusten[1,21]

The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop

E Manolis[1], S Rohou[2], R Hemmings[1,3], T Salmonson[1,4], M Karlsson[5] and PA Milligan[6]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Objectives:
- To promote "Good Practices" with regards to the planning, conduct & documentation
- To provide illustrative examples to demonstrate their use, impact & value
- To promote Model Informed Drug Discovery & Development (MID3)

Review and Input from MSWG:
- Efthymios Manolis (EMA/MSWG)
- Terry Shepard (MHRA/MSWG))
- Ine Skottheim-Rusten (NMA/MSWG/PDCO)

CHMP Sponsors:
- Tomas Salmonson (MPA/CHMP chair)
- Rob Hemmings (MHRA/CHMP/SAWP)

Abstract:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/abstract
Paper:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf
Supplemental info:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/suppinfo
Podcast:
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2163-8306/homepage/podcasts.htm

MID3 Framework: Key Elements

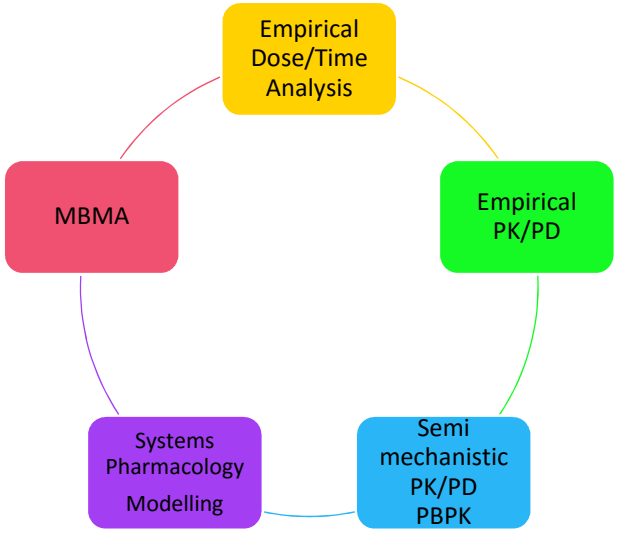
Strategic Questions & Planning

- Medical Need / Commercial viability
- Pharmacokinetics
- Efficacy
- Safety/Tolerability
- Benefit/Risk
- Clinical viability
- Study and Program design

Level(s) of activities

- **Compound Level**
- **Mechanism Level**
- **Disease Level**

MID3 Approach(es)



Documentation :

Analysis plan	Simulation plan	Report
• Introduction	• Introduction	• Synopsis
• Objectives	• Objectives	• Introduction
• Data plan	• Additional information	• Objectives
• Data exploration	• Methods	• Data
• Methods	• Assumptions	• Methods
• Assumptions		• Assumptions
		• Results
		• Applications (prediction/simulation)
		• Discussion
		• Conclusions
		• Appendix

Assumptions:

Type of Assumptions
• Pharmacological
• Physiological
• Disease
• Data
• Mathematical and statistical

Impact :

Impact on Internal decision

HIGH CATEGORY IMPACT
REPLACE - MID3 approach provides inference which informs internal decisions without requiring additional experimental or trial data to be generated

MEDIUM CATEGORY IMPACT
INFORM - MID3 approach provides inference which informs internal decisions

LOW CATEGORY IMPACT –
DESCRIBE - MID3 approach provides inference which has limited impact on internal decisions

EFPIA MID3 Good Practice White Paper:

- **Appears to have been well received**
  - One of the most accessed and cited PSP articles over past two years
- **Socialised via Scientific meetings**
  - CP/ PMX: EU -PAGE, US- ACOP, Japan -JCPT / PAGJA /JSSX (2017), China -ISQP, ICSA /IDDST
  - Statistical: PSI/ EFSPI, ASA , Common Best Practice publication (2017)
  - Regulatory: DIA, TOPRA
- **Ongoing Regulatory Engagement**
  - EMA: MSWG + CHMP, Dosing finding workshop, Extrapolation workshop, PBPK workshop
  - FDA: OCP
  - ICH: Potential for standalone MIDD/ MID3 guideline
- **Does interest match with actual practice and expectation?**


Original Articles

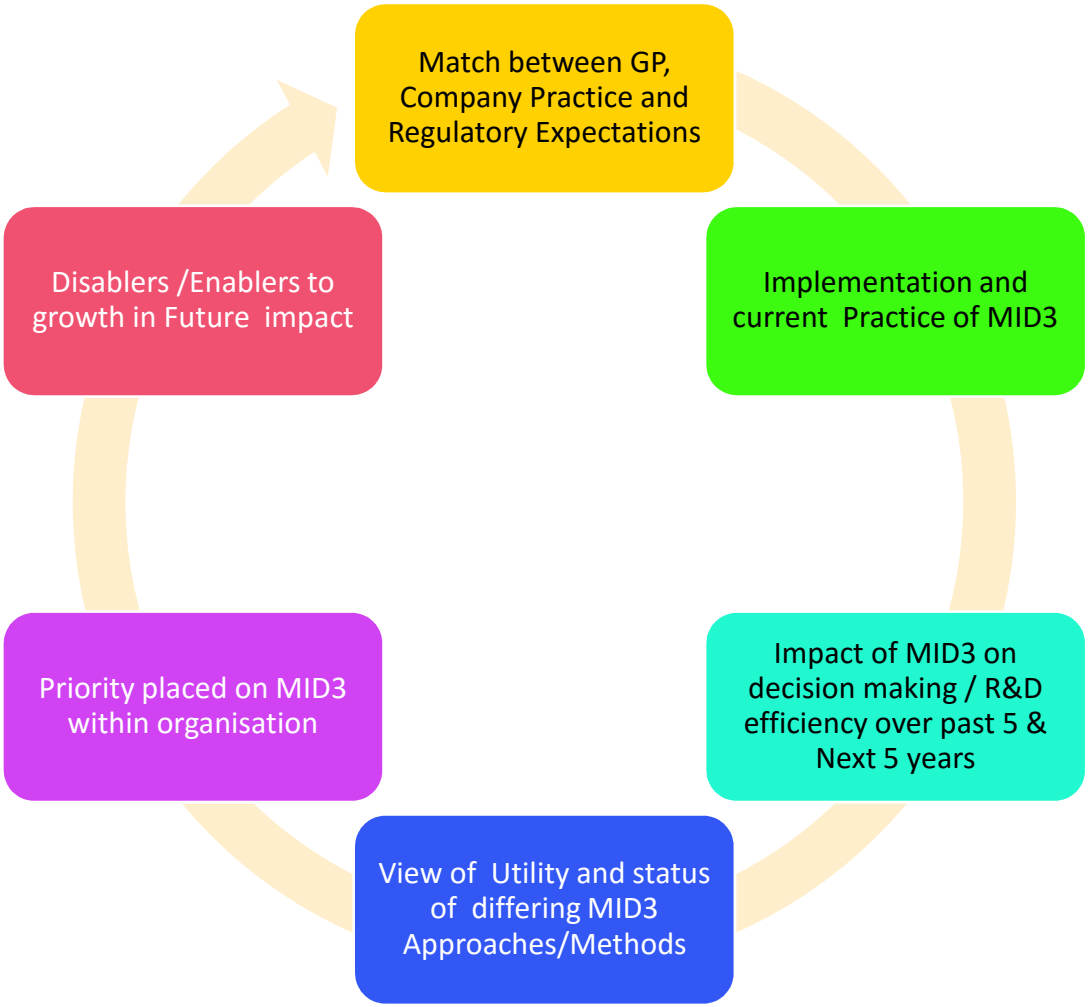
Common Best Practice in Modeling & Simulation across Quantitative Disciplines: A Comparison of independently emerging Proposals

Sandra A.G. Visser, Jonathan D. Norton, Scott Marshall & Michael O'Kelly

Page 00 | Received 30 Nov 2016, Accepted 20 Sep 2017, Accepted author version posted online: 29 Sep 2017

Journal
Statistics in Biopharmaceutical Research
Latest Articles

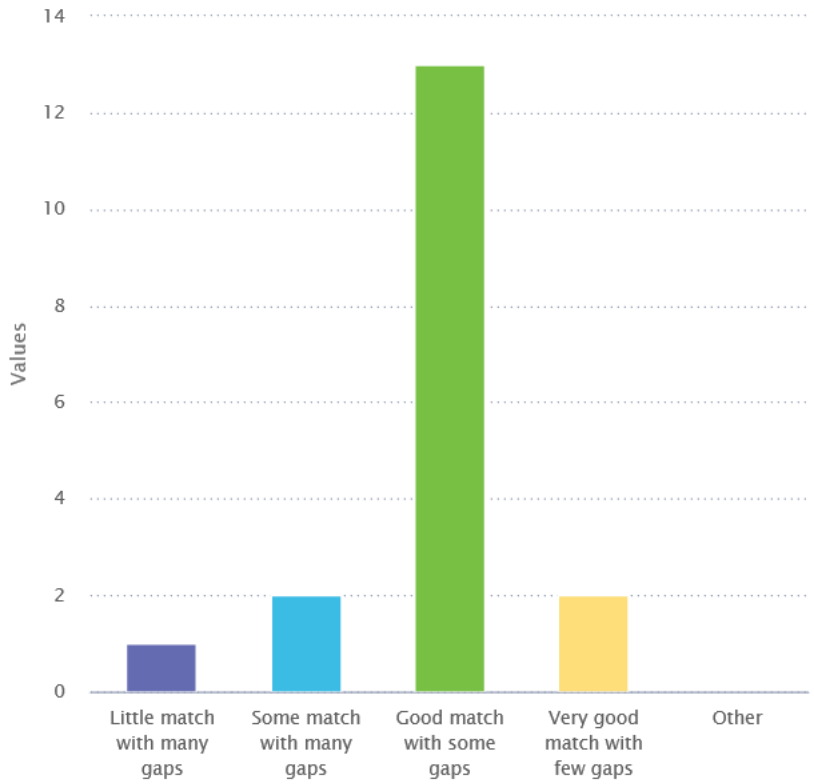
MID3 Good Practice Questionaire Topics



- Circulated to PhRMA (MIDD) & EFPIA (MID3) Clin Pharm/ PMx Reps (N=18 from 23)
- Completed by EMA and FDA

Match between GP, Company Practice and Regulatory Expectations

How close do the recently documented MID3 good practice match with Regulatory Expectations /Company practices ?



Match

- Ethos, Strategic approach and similar Documentation Practices becoming standard across many companies

Gaps (Practice)

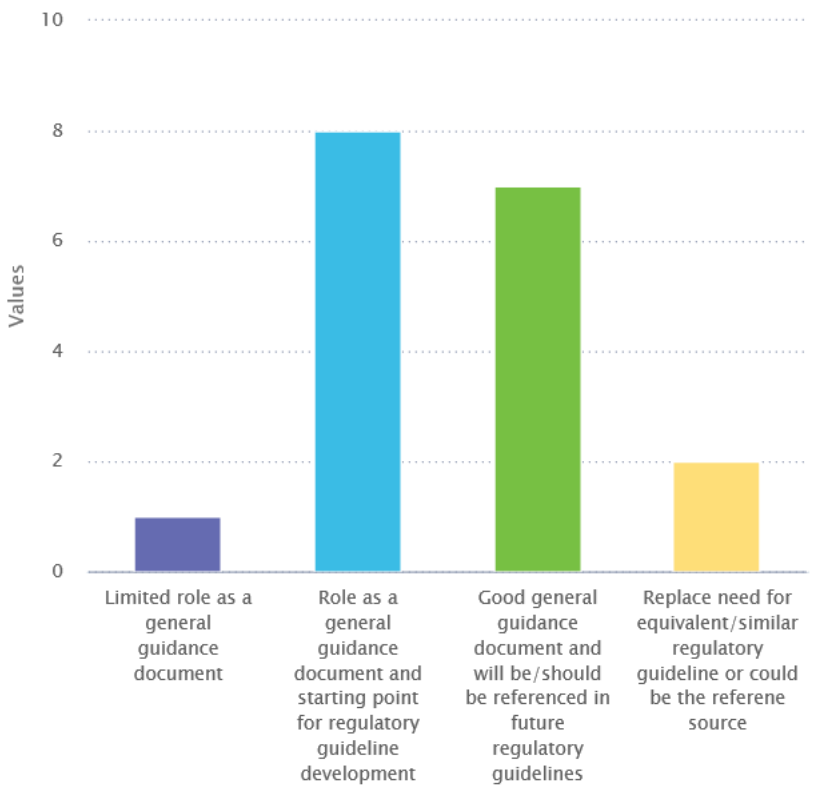
- Use of Assumption table
- Use of Impact assessment
- Consistency of application and company requirement/ request
- Regulatory guidelines and consistency of interactions

Gaps (GP Document)

- Greater emphasis on reproducible research

Match between GP , Company Practice and Regulatory Expectations

To what Extent should the MID3 good practices serve as a Regulatory Guideline for the industry?



- Good general guidance & Starting point
- Inspires the need for a similar regulatory guidelines
- Need separate technical guidelines to cover applications and approaches

Implementation and Current Practice of MID3

Modest (~50%) to Substantial (~50%) increase in Organisational Structure, Application and Process

- Growth : Evidence of industrialisation, Strategic planning more common, greater implementation of wide range of application approaches and particular growth in some disease areas/populations e.g. Oncology, Rare disease and Paediatrics.
- Limitations: Skillsets, influence of decision-makers and regulatory leads

Impact of MID3 on decision making / R&D efficiency over past 5 & Next 5 years

Modest (30/40%) to Substantial (50/60%) increases in Past /Next 5 years

- Change : Organisational Expectation
- Limitations: Inconsistency of regulatory response to MID3 submissions
- Challenges: Establishing and maintaining the level of data integrations, routine application of quantitative approaches across ever more complex and changing portfolios including business development
- Enablers : Regulatory guidelines, reproducible research and automation

View of Utility and status of differing MID3 Approaches/Methods

	A) A mature methodology that will do little to significantly further advance R&D efficiency	B) A mature methodology that is starting to fulfil its promise with respect to advancing R&D efficiency	C) A growing methodology that is expected to do little to significantly further advance R&D efficiency	D) A growing methodology that is starting to fulfil its promise with respect to R&D efficiency	Other
MID3 General		10%	10%	**75%**	5%
Empirical dose/time exposure response	22%	**50%**		28%	
Empirical PK/PD	17%	**61%**	6%	17%	
MBMA		17%	17%	**56%**	11%
Semi Mechanistic PK/PD		28%		**72%**	
PBPK	6%	**56%**	11%	28%	
Systems Pharmacology			33%	**61%**	6%

Priority placed on MID3 within organisation

Some (39%) , Set by regulatory expectations (39%), High (22%)

- Believe that regulators should position MID3 very high in their priorities
- Late stage and submission use of MID3 needs to be driven by regulators.

  This in turn will increase early stage utilisation.
- Regulatory feedback on MID3 is very impactful with decision makers
- Some sponsor (leaders) will not see value of MID3 unless regulators require it
- Clarification of what is acceptable to regulators is required

Disablers /Enablers to growth in Future impact

	Pharma	
	Disabler	Enabler
Structure/focus /awareness	1	1
Acceptance of MID3 approaches	2	2
Environment	5	6
Resources /Budget	4	4
Evolution of R&D/regulatory Process	3	3
Process & Guidance	6	4
Technical advancement	7	6
Other		

- Hard to rank but top 3 separate out
- CP/PMx and stats need to come together to move this forward
- Better alignment between Pharma and regulators is required

Summary

- MID3 Good Practice matches well to company practices and it should serve as a general guidance and starting point/ reference for future regulatory guidelines
- Moderate to Substantial growth in implementation is reported
- Moderate to Substantial growth in Impact has occurred in past 5 year and is expected to continue into the future !
- A mixed view with respect to organisational priority on MID3 is reported
- Enablers/Disablers highlight the need to address the interplay between organisational priority, acceptance of the approaches and Regulatory guidance /leadership

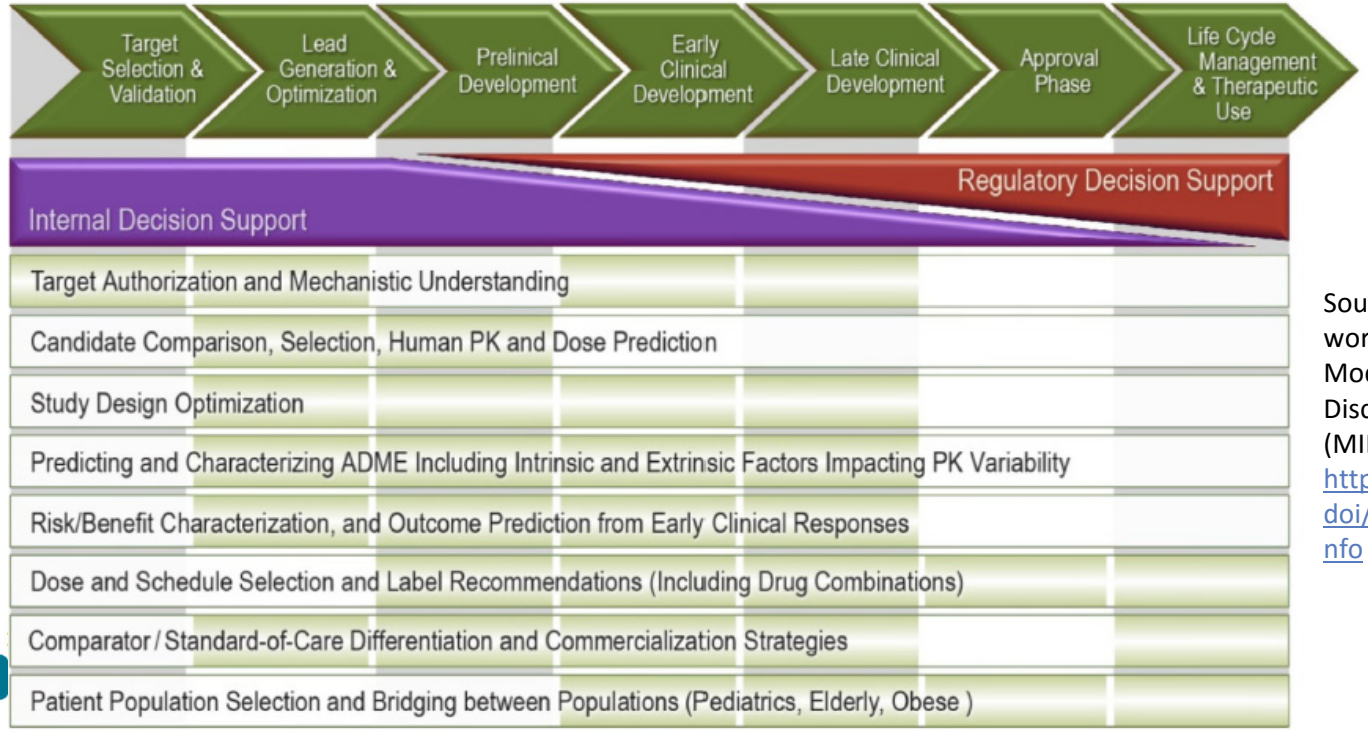
Acknowledgements

- EFPIA MID3 work group colleagues who helped develop the survey!
- Thank you to all Survey Participants !!

Applications of MID3 in Public Domain

- **About 100 case studies arranged by Application Type and R&D stages**
  - ~30 exemplified in document
- **Summarised by:**
  - Key themes
  - Activities levels
  - Modelling approach
  - R&D questions
  - Internal impact and decision making

- Sourced from PUBMED and the EMA/EFPIA M&S workshop
- Does not pretend to be an exhaustive overview of each application



Source: EFPIA MID3 workgroup: Good Practices in Model-Informed Drug Discovery and Development (MID3) http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/suppinfo

Assumption Setting, Evaluation, Impact Assessment: Examples

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological assumption Asymptotic Emax model fixed to 100% is a more physiological description of the data compared to linear model	For this drug class, across the dose range studied, Emax of 100% is more realistic	New	Testable with a wider range of concentrations (external/ future study)	Comparison of simulated metrics of interest between the two competing models	To achieve a 90% response (assumed to be clinically meaningful) requires a twofold higher dose using the Emax model compared to the linear model. ➔ Test doses suggested by Emax model in Phase 2
Physiological assumption No difference in drug clearance between healthy subjects and patients	Patients with major depression disorders are as healthy subjects (in regard of ADME/PK features) once age and weight are taken into account	Established	Testable by pooling healthy subjects and patient data, assuming that all other qualities are exchangeable	Combined analysis with healthy subjects and patients	Combined analysis found only a 10% lower drug clearance in patients. ➔ No dose adjustment necessary for PK reasons
Disease assumption A linear progression of disease with a slope of X/year	Cannot be estimated directly from the dataset, but supported by literature review	Established	Not testable with the present dataset	Sensitivity analysis changing the value of the slope for disease progression from X to Y	i) Varying the slope by X and Y will not change the selected dose for P3 ➔ Selected dose for P3 can be implemented ii) Varying the slope by X and Y will change the selected dose for P3 drastically ➔ Three different doses should be tested
Data assumption Data below limit of quantification (BLQ) have no impact on analysis results	There are <20% BLQ concentrations after treatment	New	Testable	Run final model with BLQ using M3 method in NONMEM (Beal 2001[82]) and compare to model without BLQ	Negligible changes in parameter estimates ➔ Final model excluding BLQ observations selected
Mathematical and/or statistical assumption Similar variance in drug clearance between adults and children (2 to 12 years)	Physiological and PK knowledge	New	Not testable at the stage of predictions but can be evaluated with data from children	Sensitivity analysis on the variance value of drug clearance	i) If variance is <= 2-fold, children receiving the highest dose are in the safety range established for adults ➔ Suggested dosing can also be used in children ii) If variance is > 2-fold, children receiving the highest dose are outside the safety range established for adults ➔ Alternative dosing for use in children

See Table 5 in white paper: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf

Potential Panel Questions

- Is there a need for regulatory MID3 Guideline which captures (expands on) the Good practice framework ?
- The questioinaire findings indicate a mod to substantial growth in implementation and application of MID3 across institutions for now and the future. Does this indicate job done?
- There appears a “chicken and egg” situation when it comes to regulatory promotion (via guidelines, workshops) & acceptance of approaches vs consistent and more expansive implementation and application in Pharma. How do we address this issue?
- Is MID3 /MIDD the solution both for R&D efficiency and regulatory efficiency ?
- There were some common enablers and disablers (e.g. Structure , Acceptance) and some differing viewpoints on the importance of Regulatory guidelines vs importance of changes in the general environment (e.g. growth in consortia , availability of data). Can the panel comment further on this ?
- Can you comment on any differences in focus and emphasis with respect to process development in Pharma and Regulatory agencies ?
- Are there differing viewpoints on status and value of different MID3 approaches to R&D?
- What global regulatory MIDD/MID3 developments do we need to help drive greater consistency?
  What should a sponsor do when faced with an inconsistency?

Potential questions on FDA slides

- Will a general MIDD guideline be part of PDUFA6?
- Are there any particular elements that will be promoted?
- Where are we with regard to workshop planning, what can we expect in terms of construct, input & output? Would ongoing dialogue be possible ?
- Do you have any further update on how the pilot programs will work?

Is there a need for regulatory MID3/MIDD Guideline which captures (expands on) the Good practice framework ?

- There was indication from the majority of companies that this would be desirable. Looking for clarity in what and how much to submit. How to get efficiency / consistency within the regulatory review process
- While the MID3 framework has a slant toward regulatory submission it is geared towards R&D in general with the mind-set of improving how these approaches are implemented and practiced within pharma companies. It is geared towards helping practitioners implement their practice.
- Having a similar guideline with the elements slanted more towards regulatory expectation would be useful. It could function as a source which could be referenced by other guidelines
- Adoption of Impact and Assumption approaches could help triage of MID3 review and focus

The questioinaire findings indicate a mod to substantial growth in implementation and application of MID3 across institutions for now and the future. Does this indicate job done ?

- Certainly seems consistently encouraging across most companies, but we still seem to be some way off full model informed drug discovery and development.
- Good progress in terms of acceptance of approaches in hard to study high unmet medical need areas, but this is has not translated in to other areas.
- This does rightly or wrongly leads to the suggestion that it is acceptable only when there is no other alternatives rather than when it provides an efficient way forward for all areas and this needs to change.
- Importantly we are only really at the very beginning of using these approaches for safety prediction

There appears a “chicken and egg” situation when it comes to regulatory promotion (via guidelines, workshops) & acceptance of approaches vs consistent and more expansive implementation and application in Pharma. How do we address this issue?

- It does seem to be the biggest dilemma here. From the survey results it does seem like a small fraction of companies (who I assume with the willingness of their leaders) will push forward the boundaries and provide novel approaches, application etc for the regulators to opine on. But for the majority they feel they are constrained by what is in regulatory guidelines.
- This would suggest slow /moderate progression led by the few.
- Solutions…
  - need to find others ways of reaching company leaders /regulatory heads so they are more willing to support companies taking a risk.
  - Further environmental / consortia driven efforts to shift the boundary for use of novel methods that are outside of any particular project – This is an FDA highlighted enabler
  - Incentivise companies to take a risk perhaps the PDUFA 6 pilot programs will deliver this ?
  - Finally we need to find /establish fora to get senior regulatory /industry leaders to be talking about MIDD /MID3 . This ties in with the key enablers /disablers – related to organisational structure and acceptance of approaches

Is MID3 /MIDD the solution both for R&D efficiency and regulatory efficiency ?

- Greater focus on the assumptions and impact assessment should make the focus of review questions cleaner and clearer.
-