Benefit:Risk Optimization in the Confirmatory Space and Beyond

Scientific, Strategic and Organizational Challenges and Opportunities: An Industry Perspective

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Outline

- ASCPT Survey Review
- Short examples to illustrate opportunities and challenges
- Summary

Quantitative Benefit: Risk Assessment

- Great examples in early development (CPT. 2009 Jul;86(1):105-8)
  - Clinical utility index (CUI) approaches, e.g.
    - Diabetes (Diabetes Technol Ther. 2014 Aug;16(8):499-505),
    - Insomnia (CPT. 2009 Mar;85(3):277-82)
  - Multicriteria decision analysis (MCDA) approach in overactive bladder (CPT. 2016 Apr;99(4):442-451)
  - Joint modeling of efficacy and safety (CPT. 2013 Jun;93(6):502-14)
- Frequently applied in health technology assessments, pricing and reimbursement decisions
  - Best practices in MCDA approaches (ISPOR)

ISPOR=International Society for Pharmacoeconomics and Outcomes Research

In the confirmatory space?

Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making

PDUFA V Plan (FY 2013-2017)

Draft of February 2013

Figure 1: FDA Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

- "Some hold the view that a quantitative benefit-risk assessment encompasses approaches that seek to quantify benefits and risks, as well as the weight that is placed on each of the components such that the entire benefit-risk assessment is quantitative. This approach is typical of quantitative decision modeling. It usually requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary….."
- "There is significant concern that reliance on a relatively complex model would *obscure rather than elucidate a regulator's thinking*…."

9. Which of the following “learning” activities may be permissible in the confirmatory space?

Derive alternate/untested dosing or regimens for labeling that were not directly studied in confirmatory trials	74%
Optimization of benefit-risk profile using model-based inferences	73%
Dose restriction or modification in subpopulations or special populations (pediatrics, elderly, patients with comorbidities etc)	91%
Using exposure-response as supportive evidence of effectiveness	94%
Using exposure-response as confirmatory evidence of effectiveness in lieu of a failed primary endpoint	51%

One survey responder: You are preaching to the choir; ask this question in other forums !

10. What technical or regulatory barriers may make the acceptance and utilization of such ad-hoc approaches difficult ?

Post-hoc analyses are exploratory by definition and need to be confirmed in future trials before regulatory action can be taken	56%
Data limitations	59%
Assumption rich parametric models may be needed; the statistical properties of these methods are not well characterized for regulatory purposes.	43%
Limited regulatory guidance or precedence, or lack of consensus on suitable methodology.	75%

Other Comments on Question 10

1. Regulatory Agency consists of experts from multiple disciplines. They do not always agree or understand the methodology.
2. QPs not generating basic science data that is absolutely needed to move this field forward.
3. Communication with statisticians within companies and regulatory agencies
4. Time. Lack of sufficient time for ad-hoc M&S analysis and interpretation in the super tight submission timeline (e.g. accept "rolling submission" of these types of ad-hoc analysis may be helpful)
5. Excessive emphasis on pre-specified statistical tests in confirmatory trials rather than totality of evidence from multiple sources

11. What organizational barriers may make the acceptance and utilization of such ad-hoc approaches difficult?

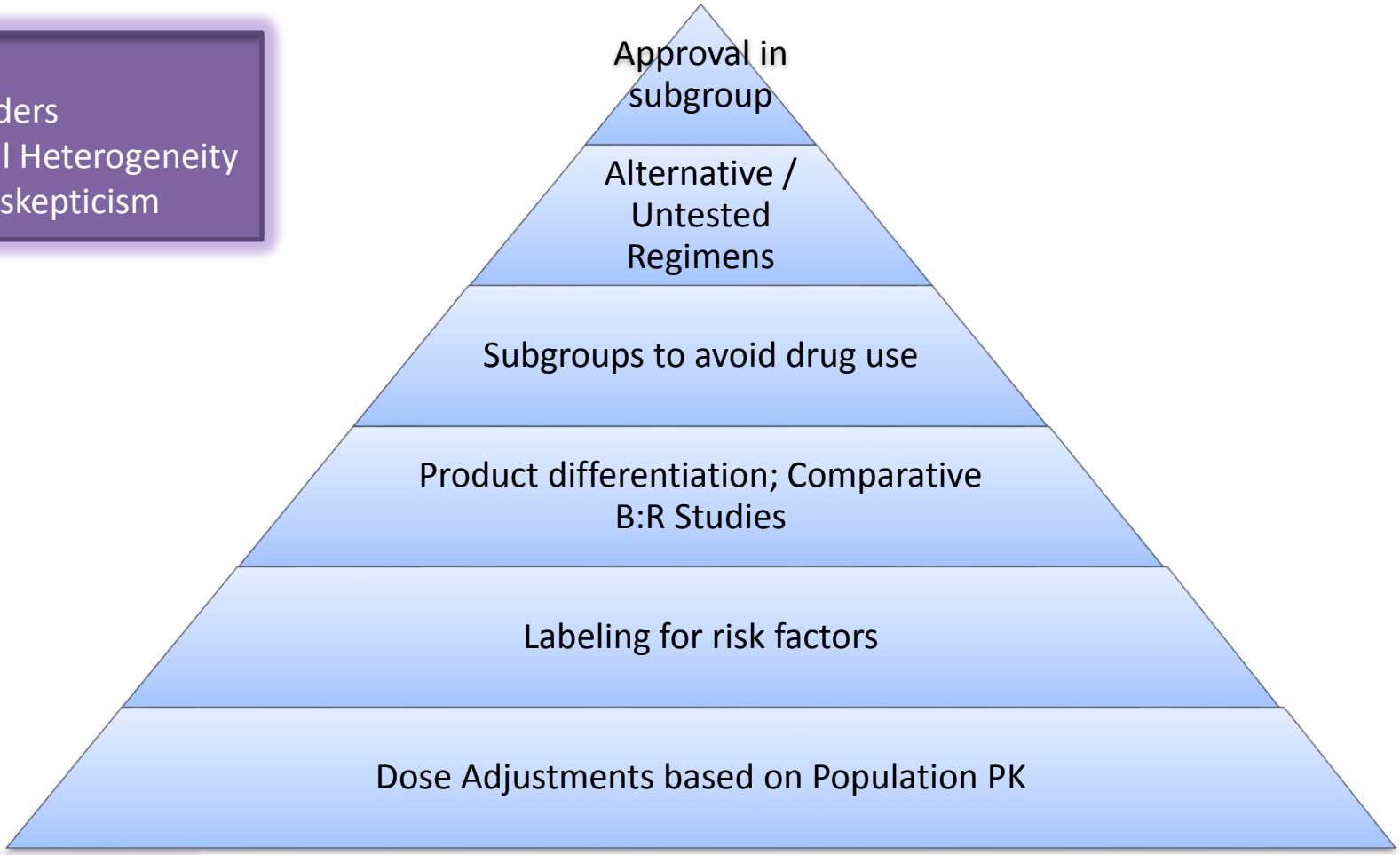
Wide-held organizational belief that approval and labeling are based on exactly how the drug was studied.	69%
Lack of awareness regarding generalization of knowledge based on data generated from trials.	55%
Lack of technical and/or strategic expertise to champion such approaches within the organization.	54%
Lack of support from senior leadership due to perceived risk	50%
Low perceived commercial valuation of alternative proposals	25%

Other comments on Question 11

1. Lack of awareness that hypothesis testing approach also involves assumptions, and the observation is not the "truth"
2. Everyone in "rushy submission" mode with limited/no interest in additional ad-hoc approaches ; same issue on the regulatory side
3. Immature / insufficient data sharing & analysis - or pooled analyses by regulators using data-on-file - on common control groups / reference treatments within an indication to add strength and robustness to the evaluation of subgroup / post hoc analyses.
4. Modelling and simulations are about averages - and the biggest challenge is population variation. Models do a huge disservice to treatment reality and individual patients

Some Areas of Influence for a Clinical Pharmacologist / Pharmacometrician

- More complex
- Many stakeholders
- Methodological Heterogeneity
- Organizational skepticism



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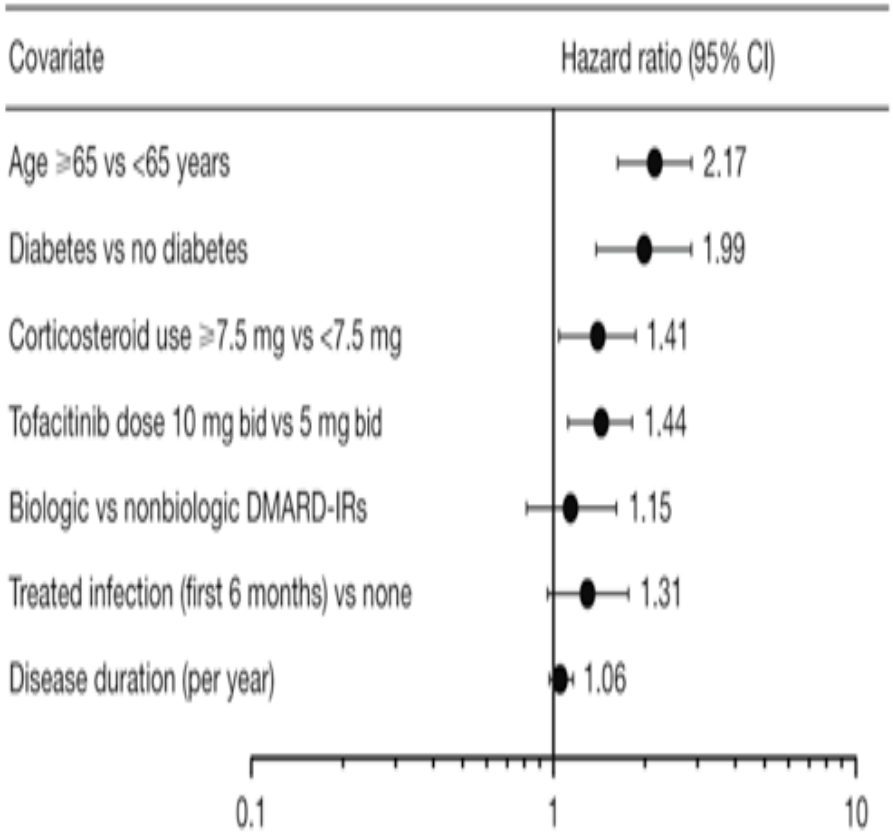
Dose Adjustments based on Population PK is a well-accepted form of B:R optimization

- Population PK is now "standard" in NDAs/BLAs
  - Dose adjustments (or lack thereof) for demographic, disease factors, and DDIs
  - Individual patient exposure for E-R analyses
- Information from *non-randomized subgroups* not a barrier to deriving dosing modifications/decisions as long as physiologically sound

Dykstra et al, J Pharmacokinet Pharmacodyn. 2015 Jun;42(3):301-14.
Reporting guidelines for population pharmacokinetic analyses.

Risk Factors of Safety Outcomes…an under-applied aspect of B:R optimization?

- Fairly common in the literature (e.g. cox PH models)
- Opportunity: seldom seen in product labels; systematic approach to supporting B:R optimization and informing prescribers; extension of SCS
- Challenge: screening/identification vs. quantifying effects of "known/expected" factors (patient, disease, geographic, design etc.);



Cohen S et al, Arthritis Rheumatol. 2014 Nov;66(11):2924-37

SCS: summary of clinical safety

B:R optimization via Product differentiation

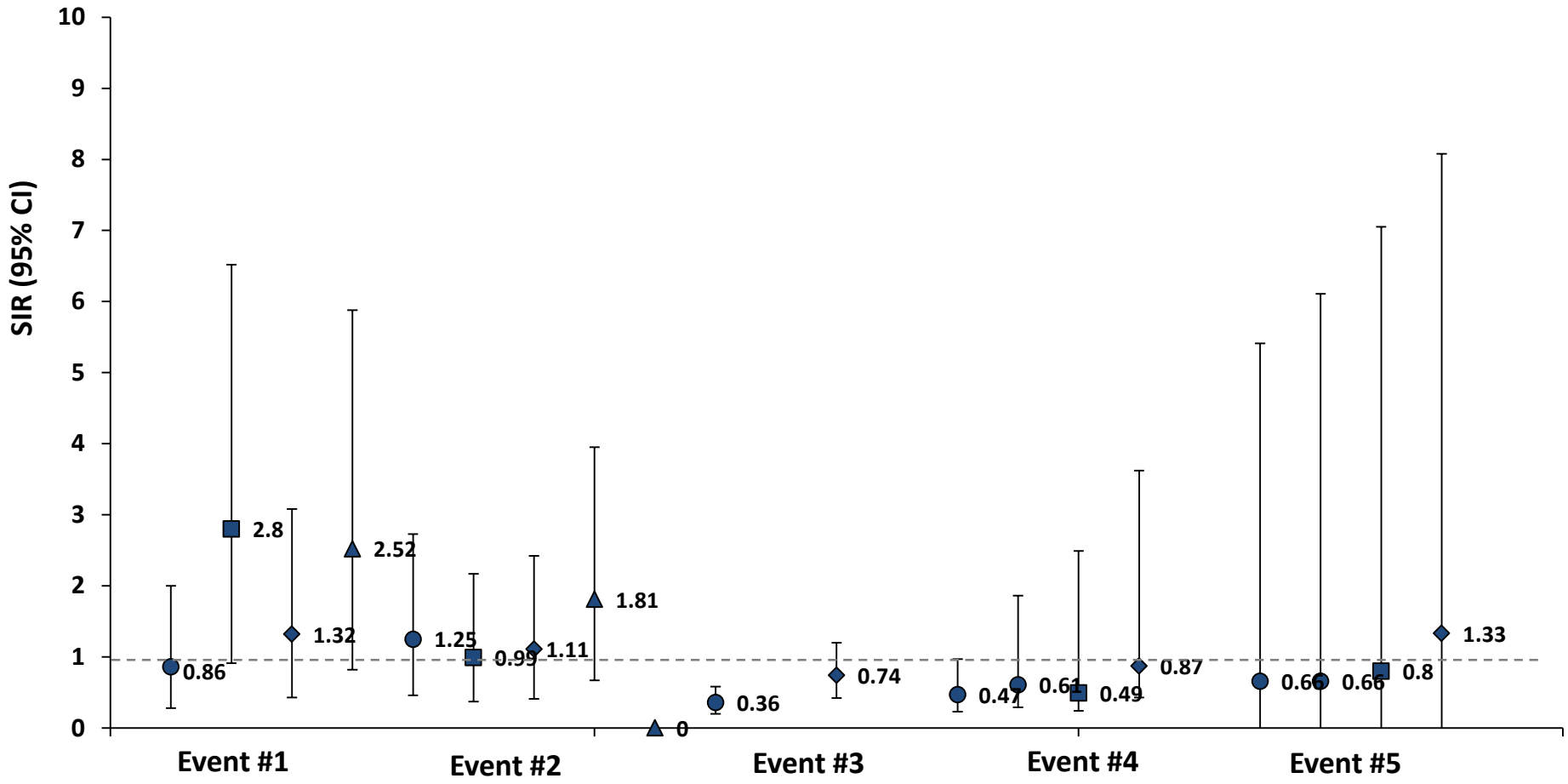
MBMA to optimize drug use and influence pricing/reimbursement

- Situation: Anti-rheumatic therapy based on novel MOA (JAK inhibition) shows efficacy as both monotherapy and in combination with MTX; with potential for lower burden for adverse events as mono
- Question: Can mono compete / beat SoC? What is the success probability?
- Solution: Traditional and MBMA to synthesize data
- Focus: Endpoint selection and trial design; using probability of success as the trial optimization metric
- Result: High PTS hypothesized for NI; Reasonable PTS for Superiority
- Current status: 1 yr, ~1000 patient Comparative B:R Study Underway

MTX=methotrexate; PTS=P(technical success); NI=non-inferiority; SoC=standard of care

B:R Optimization via alternative data sources

Patient-matched comparisons of NME RCTs vs. Competitor Registry Data



SIR= Standardized Incidence Ratios; RCT=Randomized Controlled Trials; NME=new molecular entity

Geier et al, 2016 (Data on file)

B:R optimization via product differentiation

- Opportunity:
  - Not always about data analysis and avoiding studies; MBMA can be used to inform strategy for B:R optimization, including new studies to optimize
  - Alternative data sources (e.g. real-world but “controlled”)
- Challenges:
  - Scientific: Trials differ in design and patient population characteristics, leading to heterogeneity in the treatment effect; bias (search, selection, publication etc); MA can be misleading
  - Organizational: Multi-disciplinary effort (turf wars galore)
  - Strategic: Figuring out ‘smarter’ ways to help fill the gaps

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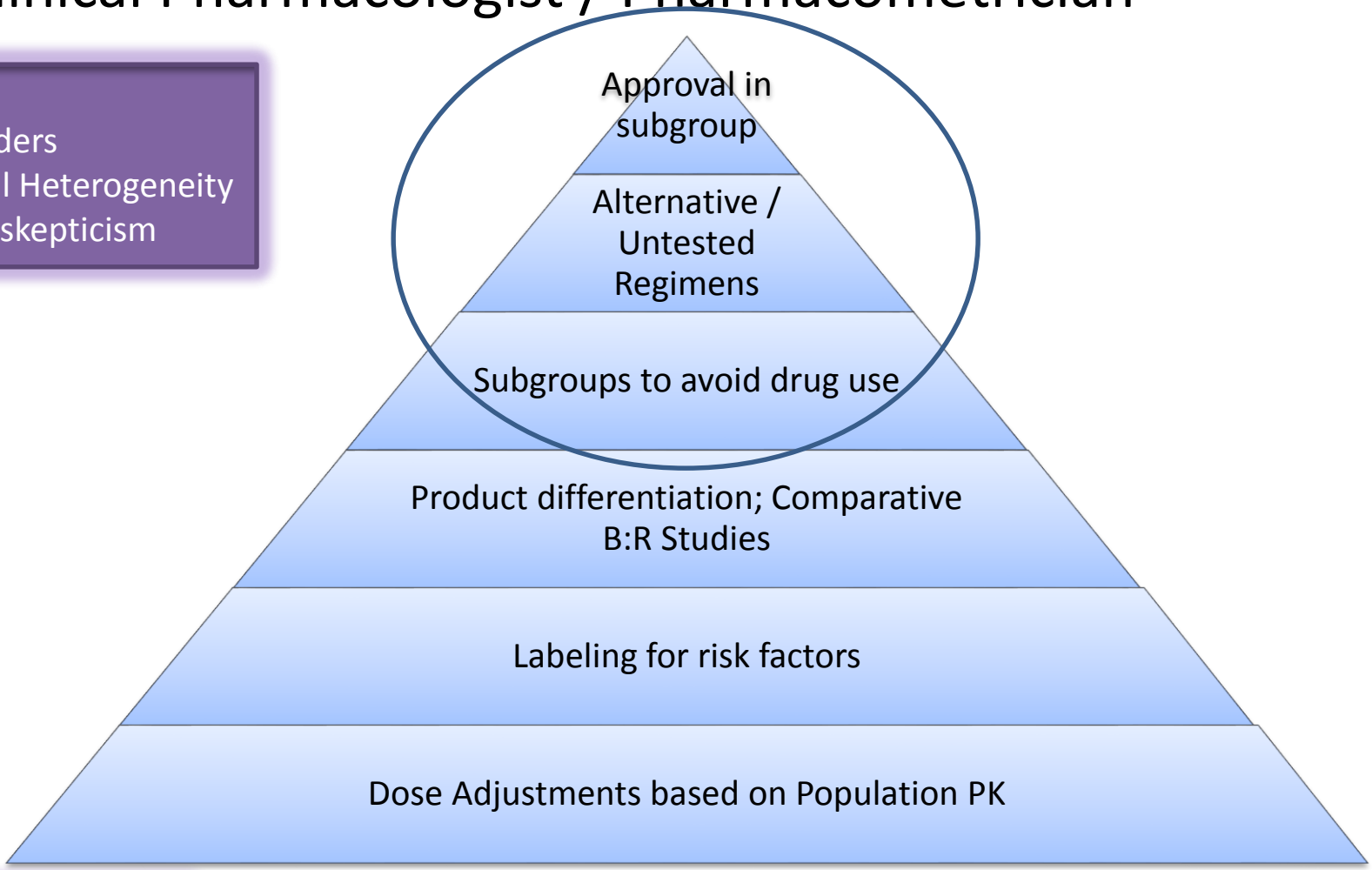

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Subgroups to avoid drug use

- Currently, predominantly qualitative and safety focused, although some efficacy examples reported
- Opportunity: To utilize model-estimated risks and assess at what point (alone or in combination with other factors) is the uncertainty in B:R too large to support use
- Challenge:
  - Efficacy: Typical analysis in the summary of clinical efficacy (SCE) involves >5 factors; Simulation studies have shown potential for high false signal rate
  - Strategically not attractive if efficacy-based

Lavange, ICDD, Feb 2016

Alternative / Untested Regimens

- "In 21 (11%) of the 198 NDA/BLA submissions that were reviewed by FDA pharmacometricians, the labelled dose was based on pharmacometric analyses, rather than being evaluated in effectiveness trials."

Table II. Alternative clevidipine dosing algorithm

Variable	Recommendation
Every 90 sec	Dose adjustment
1. If ΔSBP <50% of target	Double dose
2. If 50% of target <ΔSBP <80% of target	Maintain current dosing and wait for 3 min to reach pharmacokinetic steady state, then increase infusion rate by 1 mg/h per percentage point difference from target SBP
3. If 80% of target <ΔSBP <120% of target	Maintain current dosing
4. If ΔSBP >120% of target	Decrease infusion rate by 1 mg/h per percentage point difference from target SBP

SBP = systolic blood pressure.

Lee et al, Clin Pharmacokinet 2011; 50 (10): 627-635

Alternative / Untested Regimens (contd)

Stage	Ustekinumab Dosing
Phase 3 trials	45 mg and 90 mg
Sponsor proposed	45 mg (patients <100 kg) 90 mg (patients ≥100 kg)
FDA analysis and revised	45 mg (patients <70 kg) 67.5 mg (patients ≥70 to <100 kg) 90 mg (patients ≥100 kg)
AC Discussion and Final labeling	45 mg (patients <100 kg) 90 mg (patients ≥100 kg)

AC panel remarks:

- lack of data at 67.5 mg
- delay in generating stability data at intermediate dose
- lack of availability of information on lowest efficacious dose
- 2-tier ok for initial approval, 3-tier could be pursued post-marketing

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_SumR.pdf

Alternative / Untested Regimens (contd)

- As expected, more common in follow-on indications, pediatrics

Celecoxib Dosing in Phase 3 trial	**Weight Category**	**9-12 kg**	**13-25 kg**	**26-37 kg**	**38-50 kg**	**>50 kg**
	Suspension (3 mg/kg BID)	**25**	**50**	**75**	**100**	**150**
	Suspension (6 mg/kg BID)	**50**	**100**	**150**	**200**	**300**
Labeled Dosing Scheme	**Weight Category**	**10 - 25 kg**		**>25 kg**		
	Capsule[a] (mg BID)	**50**		**100**		

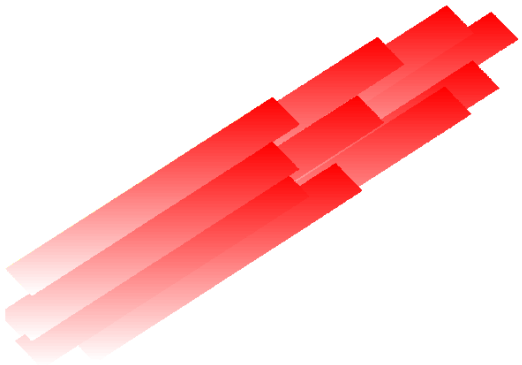
[a] – Administered Intact or Sprinkled on Applesauce

J Clin Pharmacol. 2012 Aug;52(8):1134-49

Alternative / Untested Regimens (contd)

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

- Example: Xeljanz XR
- Application: Bridging efficacy /safety data from BID to QD (from immediate to extended release) via exposure-response analysis of BID clinical and nonclinical dose fractionation data
- Result: Approval without Phase 3

Lamba et al, ACR 2015

Alternative / Untested Regimens

- Opportunity
  - Increasing trend for more than one dose in Phase 3 trials (exceptions: rare diseases / M&M outcome trials etc.)
  - Re-emphasis on importance of dose response trials; thus can inform optimization in combination with Phase 3 data
- Challenge
  - To open a dialogue at EOP2 stage and agree on framework for optimization (possibly leading to pre-specification of strategy rather than just analytical method)
    - Enhance quality of discussion via simulation-supported strategies
  - Model application vs. obsession with iterative development [complexity inversely related to utility?]
    - Can partly help address ‘rush’ syndrome

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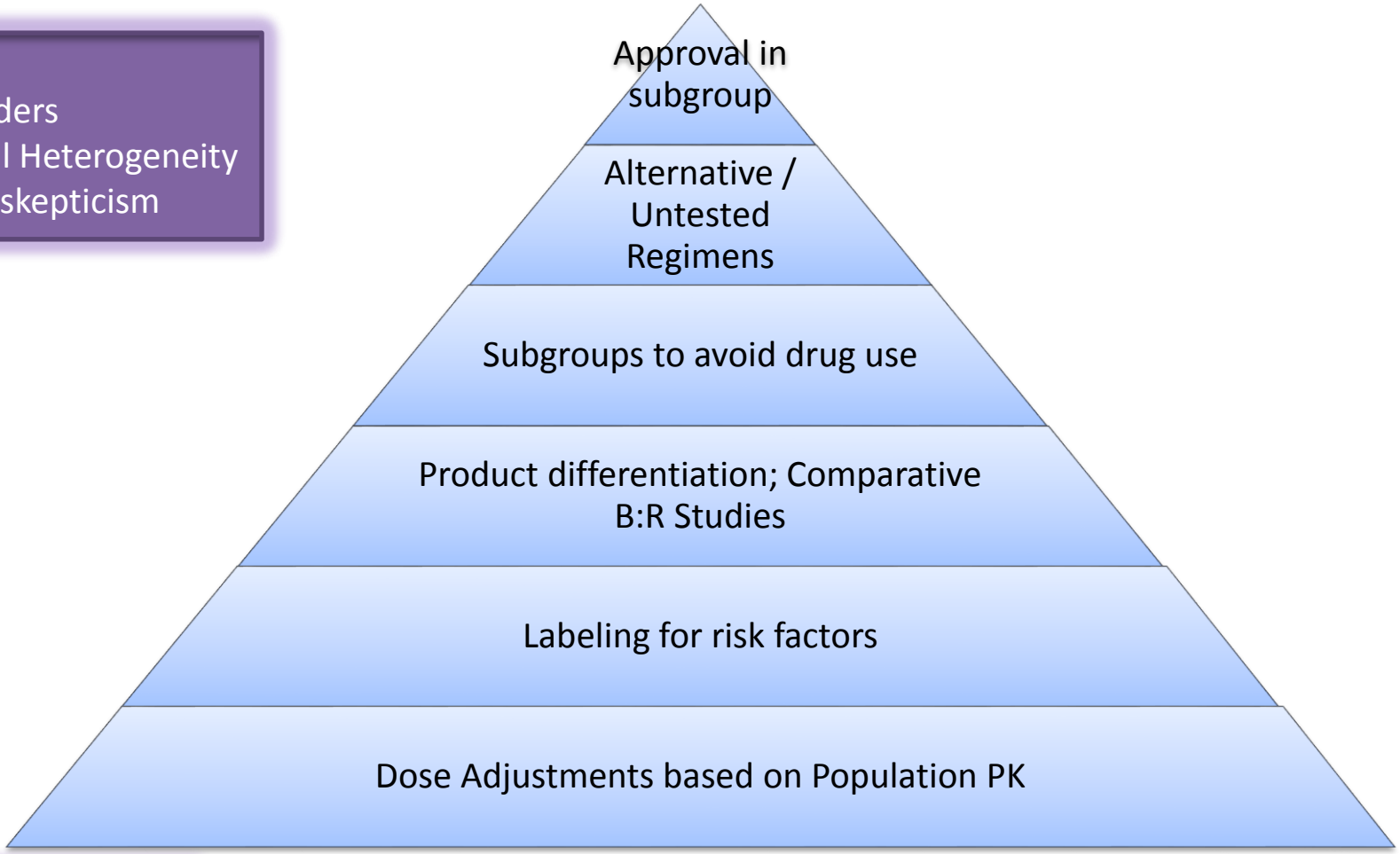

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Summary

- The ammunition is there to engage naysayers
  - Need of the hour: a collaborative effort from the community to bring it all together. Who better than ASCPT?
- Engage early with stakeholders and enhance conversation based on simulation-based strategies (prospective vs. retrospective)
- Look for alternative data sources to strategically supplement the evidence base

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