ASCPT 2016 ANNUAL MEETING
MARCH 8-12, 2016
HILTON BAYFRONT, SAN DIEGO, CA

SYMPOSIUM

Benefit/Risk Optimization in the Confirmatory Space and Beyond: Myths, Reality and Possibilities

Chairs:

Rajanikanth Madabushi, PhD, US Food and Drug Administration, Silver Spring, MD

Pankaj Gupta, PhD, Pfizer Inc., Groton, CT

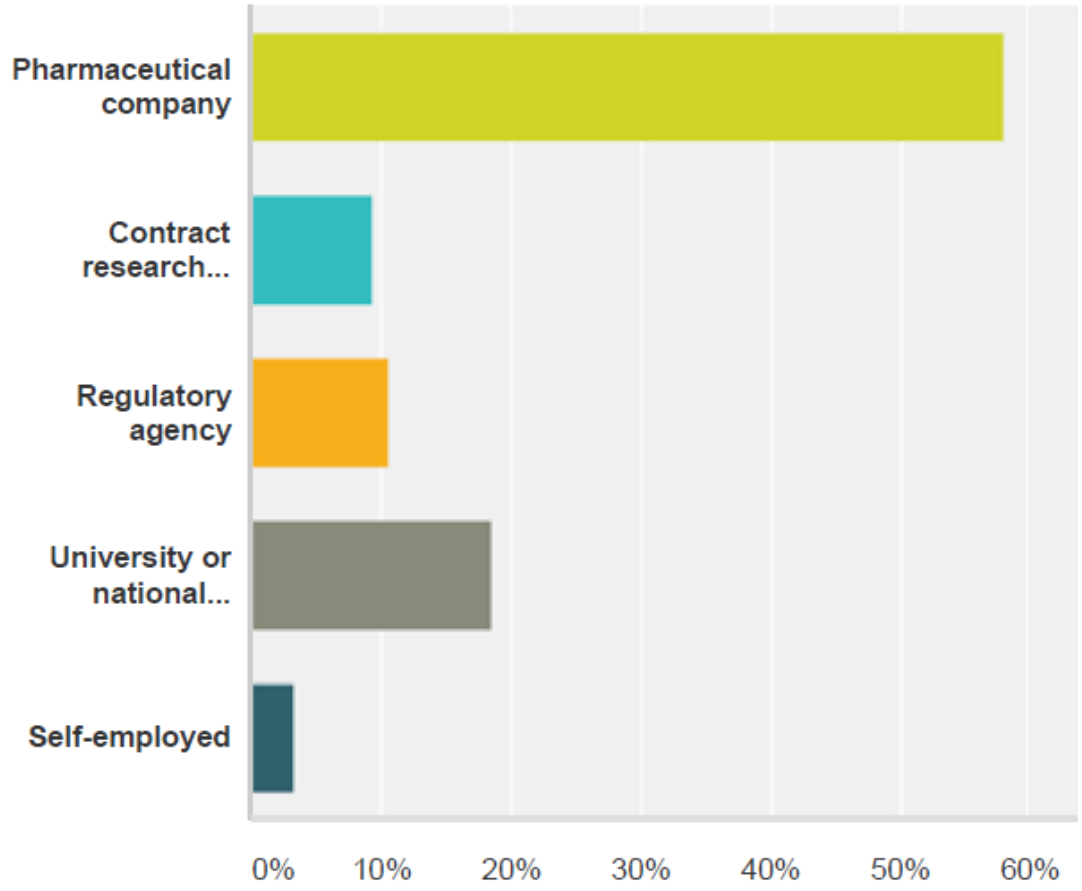
Symposium Objectives

The current symposium will discuss whether there is enough information and learning opportunities in clinical trials for marketing authorization (registration studies), that may allow for optimization of benefit/risk and inform clinical practice.

Following questions will be discussed:

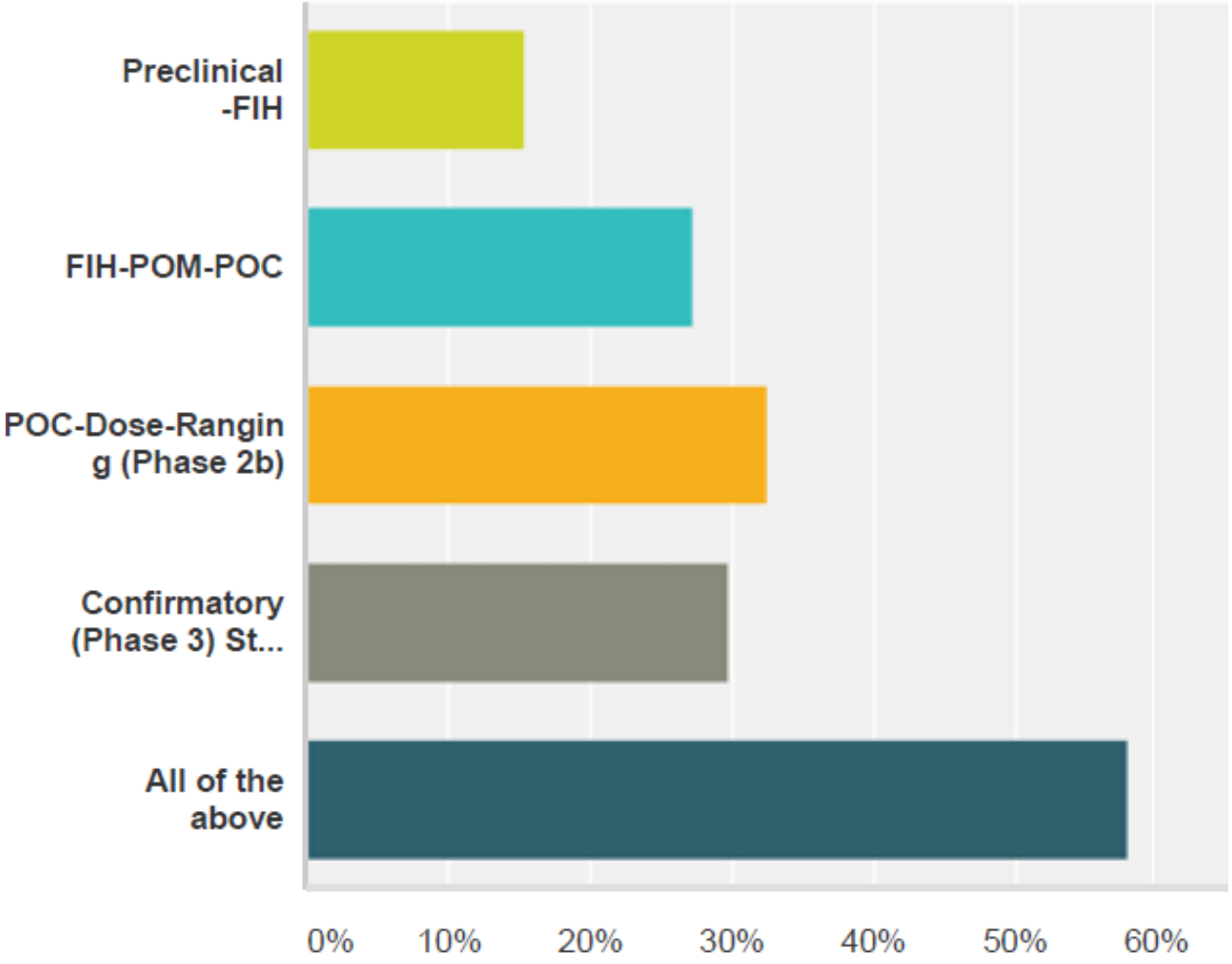
- Should findings of post-hoc exercises be considered only as hypothesis generating and require confirmatory evidence for regulatory review?
- When should post-hoc approaches be considered and what are the risks?
- Can pharmacometric analyses based on totality of available data be used to inform labeling and dosing?
- What constitutes adequate evidence in registration and post marketing studies that can allow optimization of benefit/risk and dosing?

PMK 2016 Symposia Survey Results



90% (N = 150) of the survey respondents either Clinical Pharmacologists or Pharmacometricians

80% (N = 117) of the survey respondents use M&S approaches frequently to inform decisions



Confirmatory Space: Perception Paradox

Confirmatory registration clinical trials are designed with a single key objective: to demonstrate an acceptable treatment effect on an average compared to a control of interest using a pre-specified statistical test:

Agree	61%	(70)
Disagree	39%	(44)

In general, learning from registration trials using post-hoc analyses can only be considered as hypothesis generating and require further confirmatory evidence:

Agree	30%	(34)
Disagree	70%	(81)

Speakers

- Registration Trials: Are They Meant to be Confirmatory or is Learning Allowed?
  - Joga Gobburu, PhD, FCP, MBA, University of Maryland, Baltimore, MD
- Scientific, Strategic and Organizational Challenges and Opportunities: An Industry Perspective
  - Sriram Krishnaswami, PhD, Pfizer Inc., Groton, CT
- Integration of Knowledge from Late Phase Trials to Support Regulatory Decisions
  - Yaning Wang, PhD, US Food and Drug Administration, Silver Spring, MD
- Does Pharmacometric Modeling Reliably Predict Efficacy and Safety Outcomes in Registration Trials and Can it be Utilized to Optimize Benefit-Risk?
  - Sanjay Kaul, MD, MPH, FACC, FAHA, Cedars-Sinai Medical Center, Los Angeles, CA

Panel Discussion/Q&A

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%**

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

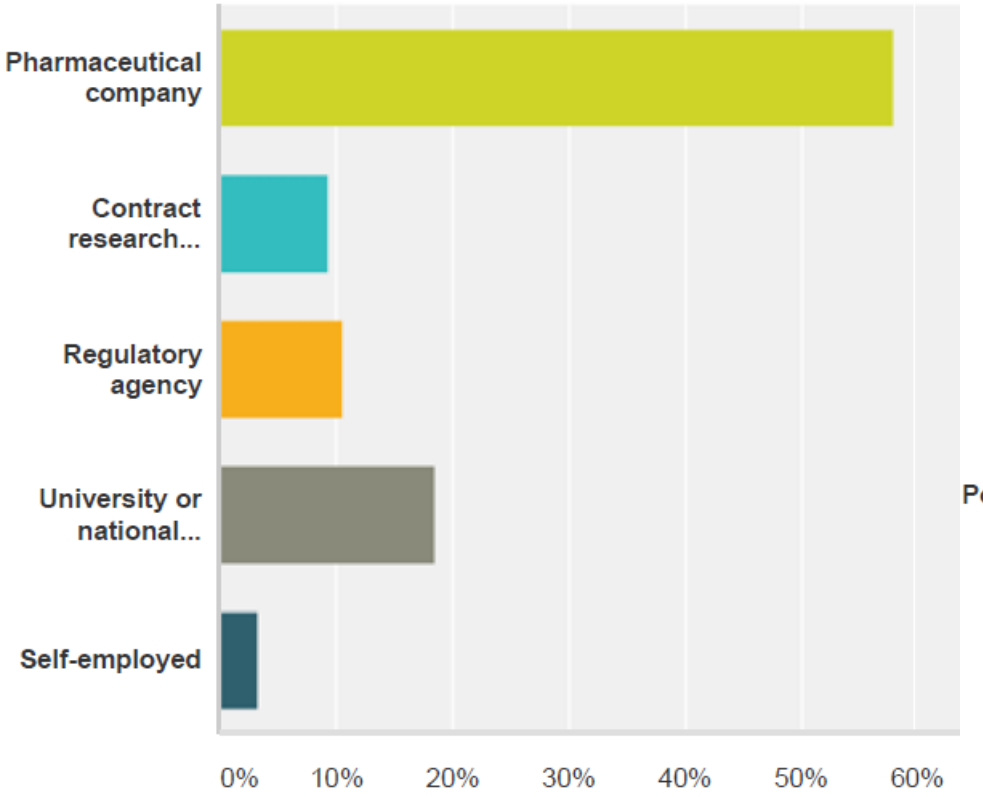
Post-hoc analyses are exploratory by definition and need to be confirmed in future trials before regulatory action can be taken	56%
Data limitations	59%
Assumption rich parametric models may be needed; the statistical properties of these methods are not well characterized for regulatory purposes.	43%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

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

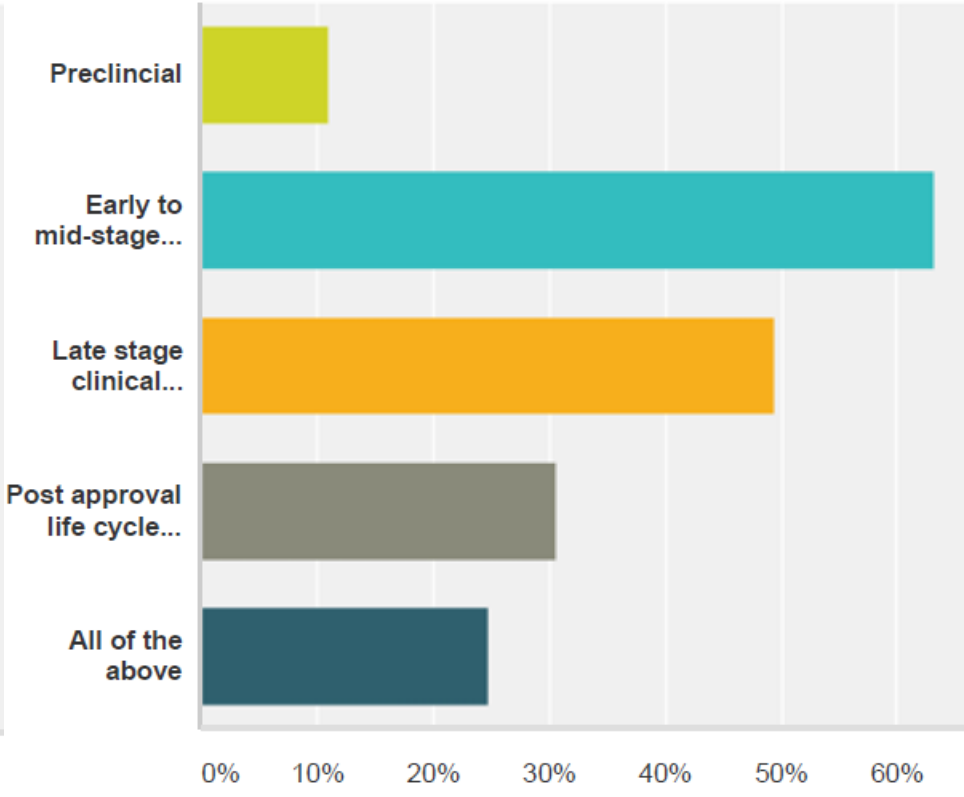
Wide-held organizational belief that approval and labeling are based on exactly how the drug was studied.	69%
Lack of awareness regarding generalization of knowledge based on data generated from trials.	55%
Lack of technical and/or strategic expertise to champion such approaches within the organization.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

PMK 2016 Symposia Survey Results

Employment (N=150)



Development Stage (N=117)



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