Animal Models of Disease for Nonclinical Safety Assessment: Pharmaceutical Industry Survey

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How Close Are We to Predicting Clinical Adverse Drug Reactions?

- Conventional toxicology studies identify the majority, but not all adverse drug reactions (ADRs) noted in the clinics
  - Olson et al. (2000): Concordance of the toxicity of pharmaceuticals in humans and in animals. *Reg Tox Pharm* 32:56-67

Less Predictable Toxicities	More Predictable Toxicities
Cutaneous	Hematologic
Neurological	Gastrointestinal
Hepatobiliary	Cardiovascular (Note: some publications indicate low predictability for CV)

- Goal – optimize predictability
  - In some instances, this may include evaluation of compounds in animal models of disease
  - Particularly for those toxicities that may be serious and not readily monitored
  - Not all toxicities will or can be predicted, even with animal models

What Do We Know About the Toxicities of "Low" Predictability?

- Low predictability anticipated because of receptors/mode of action of molecule
  - Target not expressed in conventional animal models (CAMs)
  - Molecule not well tolerated in CAMs due to physiology (e.g., antihypertensive compound in normotensive animal) – cannot dose very high

- Low predictability anticipated because of toxicity in CAM and/or human
  - Inherent low predictability of organ system
  - Inherent low predictability of particular toxicity within an organ system

Non-Oncology Adverse Clinical Drug Reactions (ADRs)

Organ System/Effect	Most Common	Somewhat Common	Less Common
Gastrointestinal	X		
Hepatobiliary	X		
Neurological	X		
Hematologic		X	
Cardiovascular		X	
Cutaneous		X	
Ocular			X
Respiratory			X
Musculoskeletal			X
Infection			X
Application Site Rxn			X

Olson et al. (2000): Concordance of the toxicity of pharmaceuticals in humans and in animals.. *Reg Tox Pharm* 32:56-67

Tamaki et al. (2013): Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. *J Tox Sci* 38(4):581-598

Non-Oncology ADRs: Prediction From Nonclinical

Moderate-High Incidence + Low Prediction – Liver, Neuro, CV, Skin

Organ System/Effect	Most Common	Somewhat Common	Low Predictability	High Predictability
Gastrointestinal	X			X
Hepatobiliary	X		X	
Neurological	X		X	
Cardiovascular		X	X	
Cutaneous		X	X	
Hematologic		X		
Ocular				X
Respiratory			X	
Musculoskeletal			X	
Infection				X
Application Site Rxn				X

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Oncology Adverse Clinical Drug Reactions (ADRs)

Organ System/Effect	Most Common	Somewhat Common	Less Common
Infection	X		
Nausea/vomiting	X		
Febrile neutropenia	X		
Anemia		X	
Mucositis		X	
Diarrhea		X	
Thrombocytopenia			X
Peripheral neuropathy			X
Constipation			X
Hepatobiliary			X

Sharma et al. (2015): Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital. *Perspect Clin Res* 6(2):109-115

Oncology ADRs: Prediction From Nonclinical

Superior Prediction vs. Non-Oncology – More Common ADRs?

Organ System/Effect	Most Common	Somewhat Common	Less Common	High Predictability	Low/Moderate Predictability
Infection	X			X	
Nausea/vomiting	X			X	
Febrile neutropenia	X			X	
Anemia		X		X	
Mucositis		X			X
Diarrhea		X		X	
Thrombocytopenia			X	X	
Perip. neuropathy			X		X
Constipation			X		X
Hepatobiliary			X		X

Sharma et al. (2015): Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital. *Perspect Clin Res* 6(2):109-115

Schein et al. (1970): The evaluation of anticancer drugs in dogs and monkeys for the prediction of qualitative toxicities in man. Clin Pharm Ther 11(1):3-40

ADRs and Prediction from Nonclinical

Is There Variation in Predictability Within Organ System Findings?

Overall Predictability	Organ System	Individual Findings: Low Predictability	Individual Findings: High Predictability
Lower Predictability (< 60%)	Hepatobiliary	?	?
	Neurological	?	?
	Cardiovascular	?	?
	Cutaneous	?	?
Higher Predictability (> 60%)	Hematological	?	?
	Ocular	?	?
	Gastrointestinal	?	?

Tamaki et al. (2013): Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. *J Tox Sci* 38(4):581-598

ADRs and Prediction from Nonclinical

Is There Variation in Predictability Within Organ System Findings?

Overall Predictability	Organ System	Individual Findings: Low Predictability	Individual Findings: High Predictability
Lower Predictability (< 60%)	Hepatobiliary	Bilirubin, ALP, LDH	Transaminases (esp. AST)
	Neurological	Fatigue, headache, dizzy	Somnolence, dyskinesia
	Cardiovascular	↑ Blood pressure	↓ Blood pressure
	Cutaneous	Urticaria, alopecia, eczema, rash, itching	Erythema
Higher Predictability (> 60%)	Hematological		
	Ocular		
	Gastrointestinal		

Tamaki et al. (2013): Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. *J Tox Sci* 38(4):581-598

ADRs and Prediction from Nonclinical

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	Neurological	Fatigue, headache, dizzy	Somnolence, dyskinesia
	Cardiovascular	↑ Blood pressure	↓ Blood pressure
	Cutaneous	Urticaria, alopecia, eczema, rash, itching	Erythema
Higher Predictability (> 60%)	Hematological	Eosinophil or WBC ↑	RBC ↑/↓ or WBC ↓
	Ocular		
	Gastrointestinal	Amylase increases	Fecal changes, emesis, decreased appetite

Tamaki et al. (2013): Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. *J Tox Sci* 38(4):581-598

So – What Do We Know About Use of Animal Models of Disease (AMDs) to Help in Prediction?

- Low predictability anticipated because of receptors/mode of action of molecule
  - Target not expressed in conventional animal models (CAMs)
  - Molecule not well tolerated in CAMs due to physiology (e.g., antihypertensive compound in normotensive animal) – cannot dose CAM very high
  - AMD may well be very helpful
- Low predictability anticipated because of nature of toxicity in CAM and/or human
  - Inherent low predictability of organ system
  - Inherent low predictability of particular toxicity within an organ system
  - Utility of AMD depends on pathogenesis of toxicity – e.g., may be helpful to utilize chimeric mouse with “humanized liver”

Literature References/Guidances and AMD Use – What is Available?

- Pharmacology/efficacy
- Safety
  - Discovery
  - Development
- Recommendations/regulatory

Animal Models of Human Disease – Pharmacology/Efficacy
Examples of Publications at Survey Initiation…. "Endless"

- Fleet, J.C. (2014): Animal models of gastrointestinal and liver diseases. New mouse models for studying dietary prevention of colorectal cancer. Am. J. Physiol. *Gastrointest Liver Physiol* 307:G249–G259
- Islam MS (2013) Animal models of diabetic neuropathy: Progress since 1960s. *J Diabetes Res* 2013:1-9
- Jay GW, DeMattos RB, Weinstein EJ, Philbert MA, Pardo ID, Brown TP (2011). Animal models for neural disease. *Tox Pathol* 39:167-169
- Mizoguchi, A. (2012). Animal models of inflammatory bowel disease. *Prog Mol Biol Transl Sci* 105:263–320
- Rosenberg DW, Giardina C, Tanaka T. (2009). Mouse models for the study of colon carcinogenesis. *Carcinogenesis*. 30(2):183-196
- Rubio-Viqueira B, Hidalgo M. (2009). Direct in vivo xenograft tumor model for predicting chemotherapeutic drug response in cancer patients. *Clin Pharmacol Ther.* 85: 217-221
- Talmadge JE, Singh RK, Fidler IJ, Raz A. (2007). Murine models to evaluate novel and conventional therapeutic strategies for cancer. *Am J Pathol*. 170: 793-804
- Ward JM, Treuting PM. (2014). Rodent intestinal epithelial carcinogenesis: pathology and preclinical models. *Toxicol Pathol*. 42(1):148-61

Animal Models of Human Disease – Safety
Examples of Publications at Survey Initiation…. "Several"

- Bolon, B. and Galbreath, E. (2002). Use of genetically engineered mice during discovery and development: Wielding Occam's razor to prune the product portfolio. *Int J Toxicol* 21(1): 55-64
- Cordaro, C.J. (1989). Transgenic mice as future tools in risk assessment. *Risk Anal* 9(2):157-168
- Murray, J.M., Thompson, A.M., Vitsky, A., Hawes, M., Chuang, W.L., Pacheco, J., Wilson, S, et al. (2015). Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid spingomyelinase deficiency: the utility of animal models of disease in the toxicological evaluation of potential therapies. *Mol Genet Metab* 114(2):217-225
- Ozaki, K., Sano, T., Tsuji, N., Matsuura, T., Narama, I. (2010). Insulin induced hypoglcemic peripheral motor neuropathy in spontaneously diabetic WBN/Kob rats. *Comp Med* 60(4):282-287
- Racke, M. M., Boone, L.I., Hepburn, D.L., Parsadaiaian, M., Bryan, M.T., Ness, D.K., Piroozi, K.S., et al. (2005). Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid β. *Neurobiol Dis* 25(3):629-636

Animal Models of Human Disease – Recommendations/Regulations
Examples of Publications at Survey Initiation….Limited

- Cavagnaro, J. and Silva Lima, B. (2015). Regulatory acceptance of animal models of disease to support clinical trials of medicines and advanced therapy of medicinal products. *Euro J Pharmacol* 759: 51-62
- Morgan, S.J., Elangbam, C.S., Berens, S., Janovitz, E., Vitsky, A., Zabka, T., Conour, L. (2013). Use of animal models of human disease for non-clinical safety assessment of novel pharmaceuticals. *Toxicol Pathol* 41(3):508-518
- U.S. FDA (2015). U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM446569.pdf
- U.S. FDA (2016). U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Osteoporosis: Nonclinical Evaluation of Drugs Intended for Treatment https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455102.pdf

Animal Models of Human Disease – Overview of Industry Use
Examples of Publications at Survey Initiation….None

- So – how about a survey to see what "real life" is like?
  - Innovation and Quality (IQ) Consortium focus group – developed a survey to determine practices and perceptions across companies
  - Survey queried utilization of animal models of disease (AMDs) in discovery (typically non-GLP studies) and development (typically GLP studies)

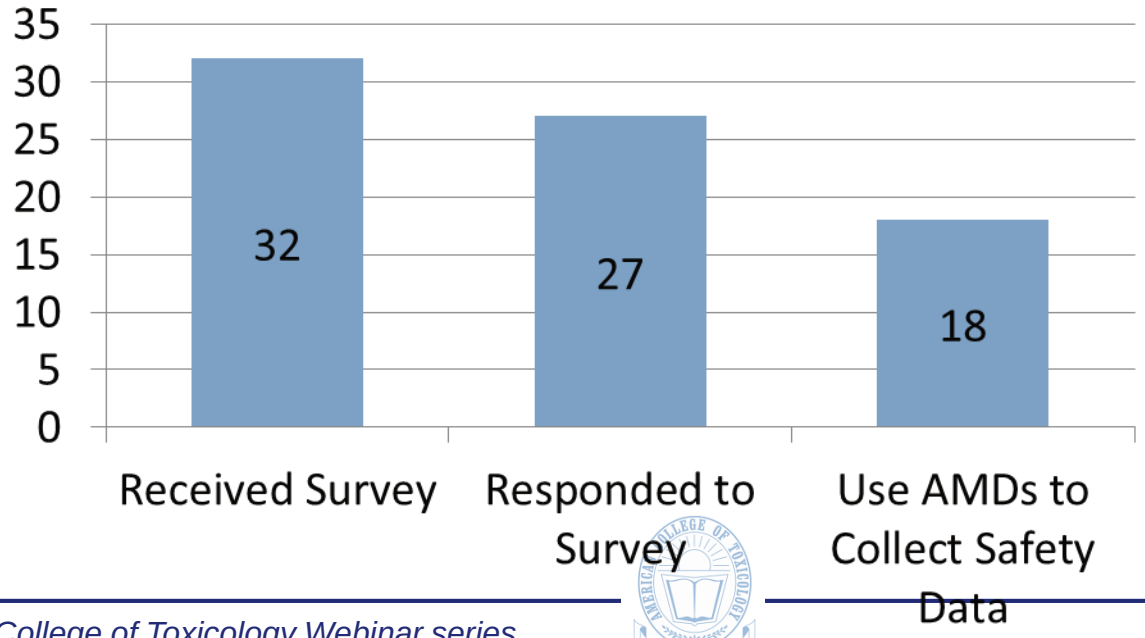
- Assumptions based on available literature information
  - AMDs in efficacy/pharmacology is widespread
  - AMDs for collection of safety information
  - Tag-on to efficacy/pharmacology/discovery studies or stand-alone studies – some use but distribution/frequency unknown

Survey Focus Group Team Members

- Jessica Couch – Genentech
- Peggy Guzzie-Peck – Janssen Research and Development, LLC
- Thomas Jones – Eli Lilly and Company
- Douglas Keller – Sanofi
- Ray Kemper – Vertex, Inc.
- Sherry Morgan – AbbVie, Inc.
- Monicah Ontieno – Janssen Research and Development, LLC
- Robert Schulingkamp – Bristol-Myers Squibb Company (currently at Johnson and Johnson Research and Development, LLC)

Survey Plan/Methods

- Cross company survey conducted by Innovation and Quality (IQ) Consortium group (DruSafe – Preclinical Safety Leadership Group within the IQ)
- Survey included queries on experience with AMDs, types of models, frequency, timing, motivation for use
- Survey distribution/response



Invited Survey Participants – 32 Members of DruSafe

AbbVie, Inc.

Agios

Alexion Pharmaceuticals

Alkermes

Allergan

Amgen, Inc.

Astellas Pharma U.S., LLC

Astra Zeneca Pharmaceuticals

Baxter Healthcare

Bayer Healthcare

Biogen

Blueprint Medicines

Boehringer Ingelheim

Bristol-Myers Squibb Company

Celgene Corporation Daiichi Sanyo

Daiichi Sankyo

Eisai, Inc.

Eli Lilly and Company

Gilead Sciences

Glaxo SmithKline

Incyte Corporation

Infinity Pharmaceuticals

Janssen Research and Development, LLC

Merck and Co.

Novartis

Pfizer

Roche/Genentech

Sanofi

Sunovion

Takeda

Teva Pharmaceuticals

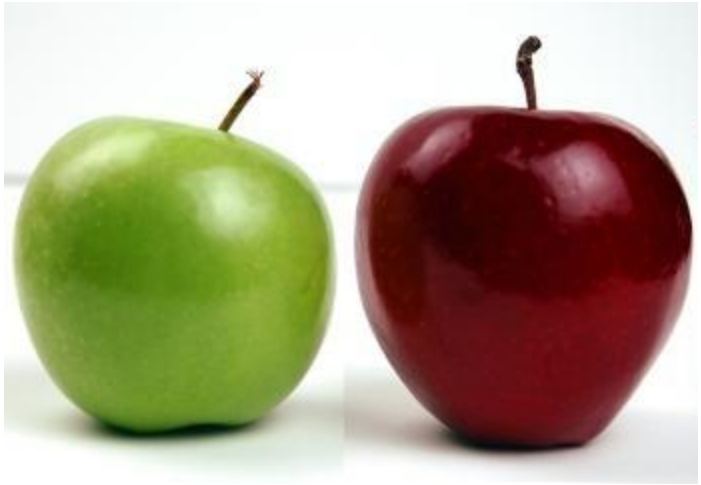
Vertex, Inc

Results of Survey – How Well Were They Predicted by Previous Recommendation Publication?

Survey Manuscript: Morgan, S.J., Couch, J, Guzzie-Peck, P., Keller, D.A., Kemper, R., Otieno, M.A., Schulingkamp, R.J., Jones, T.W. (2017): Regulatory Forum Opinion Piece: Use and Utility of Animal Models of Disease for Nonclinical Safety Assessment: A Pharmaceutical Industry Survey . *Toxicol Pathol* 45(3):372-380

VS.

Predictions/Recommendations Manuscript: Morgan, S.J., Elangbam, C.S., Berens, S., Janovitz, E., Vitsky, A., Zabka, T., Conour, L. (2013). Use of animal models of human disease for non-clinical safety assessment of novel pharmaceuticals. *Toxicol Pathol*



OR

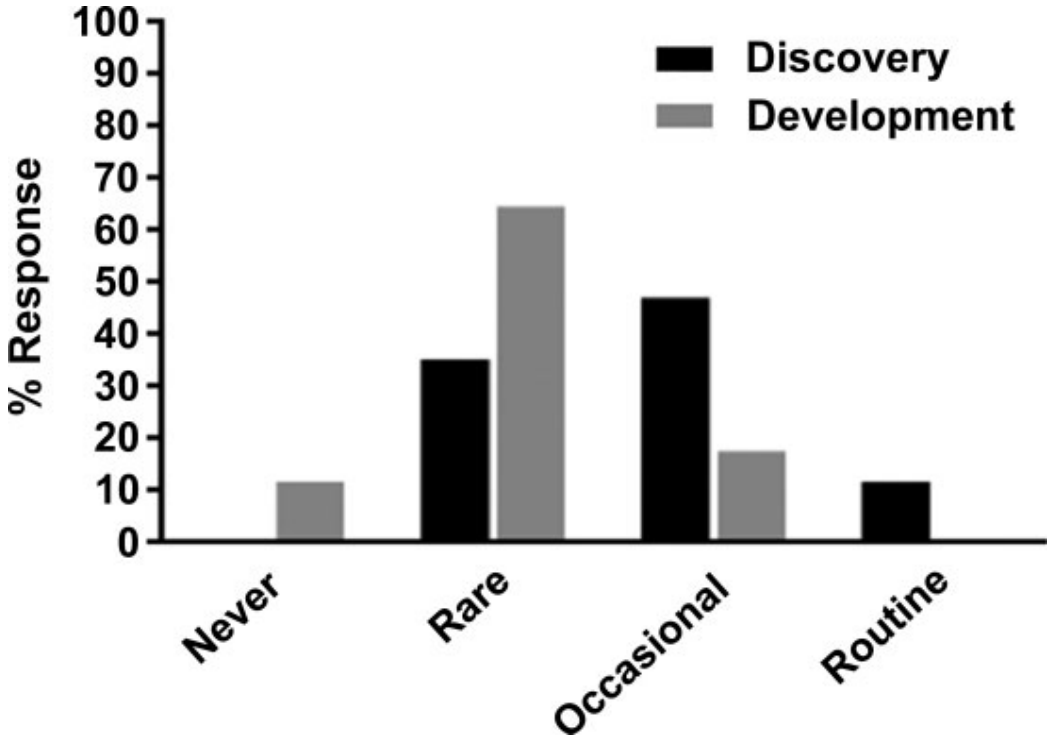
Divide Comparison into “Predictions” and “Recommendations”

- Expectations
  - Discovery vs. development – more common use
  - Therapeutic areas
  - Types of AMDs

- Recommendations
  - Use of CAMs vs. AMDs – when and why
  - Consider critical steps and risk:benefit before using AMDs
  - AMDs should be used for hazard ID/understanding and to answer specific question/hypothesis

How Well Did Predictions Reflect Current Practice?

Prediction: AMDs will be utilized more frequently in discovery vs. development



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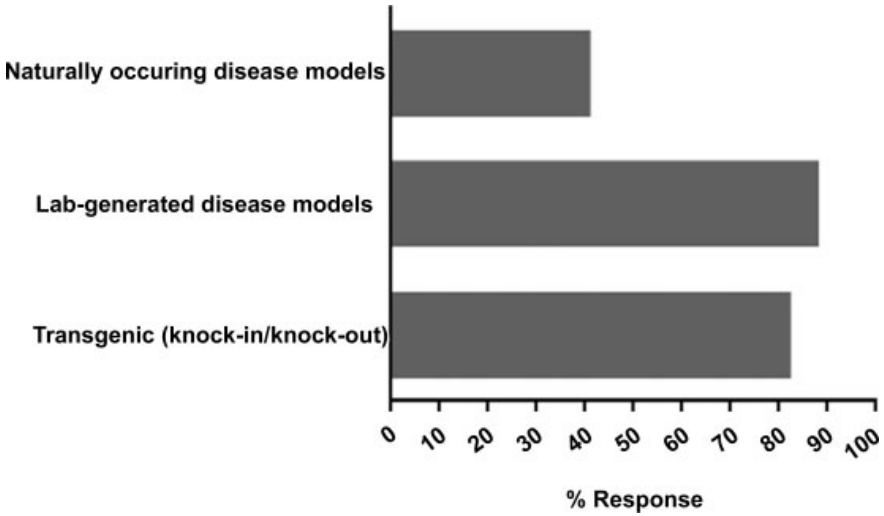
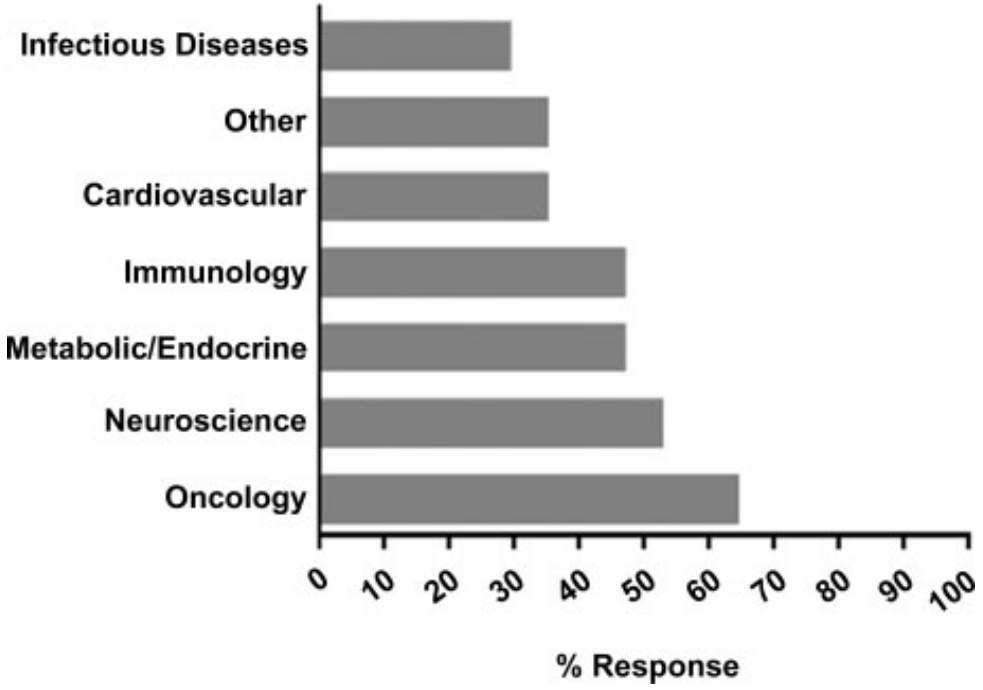
How Well Did Predictions Reflect Current Practice?

Prediction: AMDs will involve both naturally occurring and "induced" models and may be of benefit across a variety of therapeutic areas





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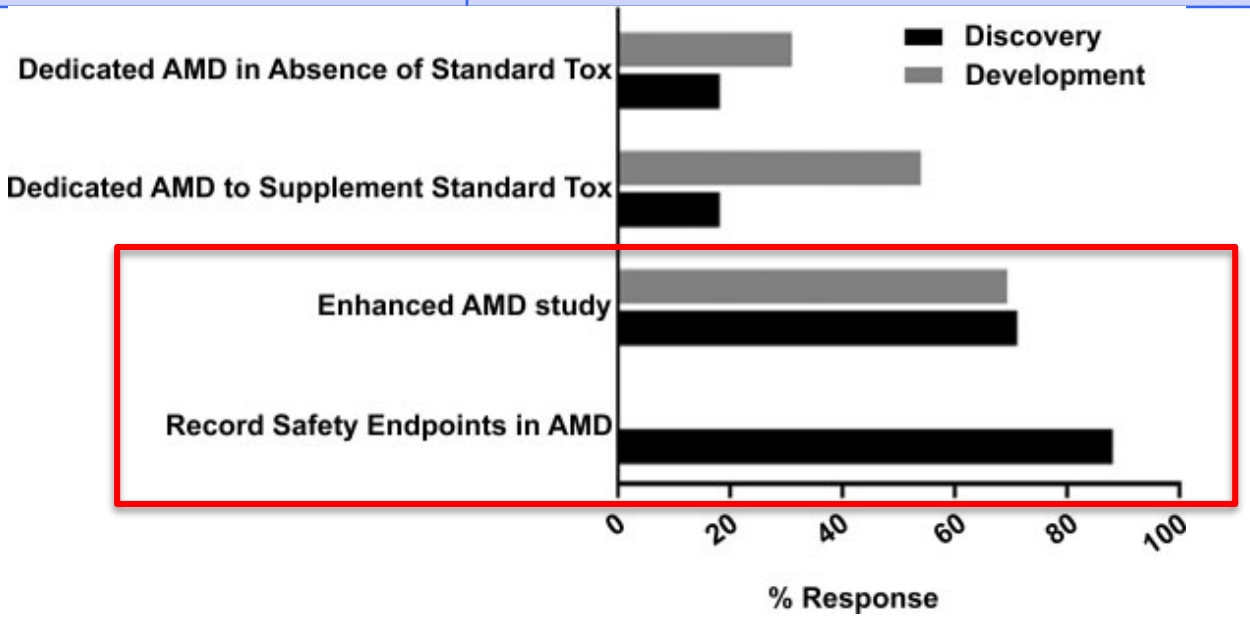
How Well Did Predictions Reflect Current Practice?

Prediction	Survey Results
Limitations of AMD in nonclinical safety testing include: • Lack of historical control • Heterogeneity in disease expression • Limited life span • Confounding effects of the disease	Most frequent concern: lack of confidence in the models and/or ability for decision-making

How Well Did Recommendations Reflect Current Practice?

Recommendations for Use	Survey Results for Use
• CAMs should continue to be utilized to further elucidate safety risks that were identified in earlier studies	• AMDs more commonly utilized to supplement, rather than replace CAMs in development • Most common use was as predicted – enhanced AMD study/record safety endpoints in AMD study



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How Well Did Recommendations Reflect Current Practice?

Recommendations for Use	Survey Results for Use (Most to Least Frequent)
• AMDs should be reserved as an adjunct to answer specific hypothesis-driven questions as it pertains to safety assessment • AMDs in safety testing should be focused on hazard identification/understanding rather than safety margin calculation	To assess potential safety concerns early prior to conduct of toxicology studies
	To de-risk or understand safety issues that may be masked by excessive pharmacology in traditional toxicology models or when target is only expressed in the disease state
	To address target or program-specific concerns that important safety issues may be missed if data were collected only using CAM
	To de-risk or understand a known clinical safety issue missed by traditional nonclinical safety models

How Well Did Recommendations Reflect Current Practice?

Recommendations for Use	Survey Results for Use (Most to Least Frequent)
• AMDs should be reserved as an adjunct to answer specific hypothesis-driven questions as it pertains to safety assessment • AMDs in safety testing should be focused on hazard identification/understanding rather than safety margin calculation	To de-risk or understand safety issues that may be masked by excessive pharmacology in traditional toxicology models or when target is only expressed in the disease state
	To address target or program-specific concerns that important safety issues may be missed if data were collected only using CAM
	Request from a global regulatory authority
	To de-risk or understand a known clinical safety issue missed by traditional nonclinical safety models

How Well Did Recommendations Reflect Current Practice?

Recommendations for Use	Survey Results for Use (Most to Least Frequent)
A rigorous risk:benefit assessment of the appropriateness of the AMD and its intended use in preclinical drug development is paramount to success	• Not directly answered, but while some had mixed results, most respondents indicated that use of AMD during development achieved their intended purpose • Responses from regulatory authorities generally favorable

How Well Did Recommendations Reflect Current Practice?

Recommendations for Use	Survey Results for Use (Most to Least Frequent)
Critical steps prior to consideration of the AMD include: • Determination of the degree of homogeneity with respect to the human disease • Rigorous characterization of the AMD	• Characterized prior to use, mostly to confirm disease phenotype • Robust information on historical controls generally not available • In some cases, thorough characterization of AMD prior to conduct of definitive studies provided information on inherent model variability and was useful toward interpretation of toxicity endpoints • In other cases, weight-of-evidence approach taken to interpret data, with consideration given to inter-animal variability within a study

Focus Team's Initial Considerations of AMDs – Limitations and Uses

Consideration	Comments
Limitations	Lack of consistent concordance between AMD and human disease
	Lack of well-characterized toxicology/pathology information in AMDs vs. conventional animal model (CAM)
Potential useful applications	More robust evaluation of toxicity when intended pharmacologic effect results in significant dose-limiting toxicity at low multiples in CAM
	Differentiation of on- vs. off-target effect (e.g., is peripheral neuropathy a manifestation of hypoglycemia rather than off-target effect)
	Evaluation of target toxicity when target is not expressed in CAM
	Follow-up investigation of unexpected toxicity in clinical investigations when not present in CAM

Overview of Results – Discovery vs. Development

- AMDs primary use is in discovery:
  - Proactive assessment of potential safety issues prior to conduct of toxicology studies
  - Better understanding of toxicities associated with exaggerated pharmacology in traditional models
  - De-risk issues when the target is only expressed in the disease state
- AMDs less frequently used in development:
  - Investigate nonclinical safety issues associated with targets expressed only in disease states and/or in response to requests from regulatory authorities

Overview of Results – Common Themes

- Optimize early data gathering and issue/hazard identification
- Prospective approach to nonclinical safety assessment
  - Target is not expressed
  - Secondary effects associated with target engagement will not occur in the absence of disease state
- Support requests/recommendations from regulatory authorities and/or internal medical exerts
- Support follow-up investigations where evaluations with CAMs failed to demonstrate toxicity signals that were identified in a clinical setting

Acknowledgements

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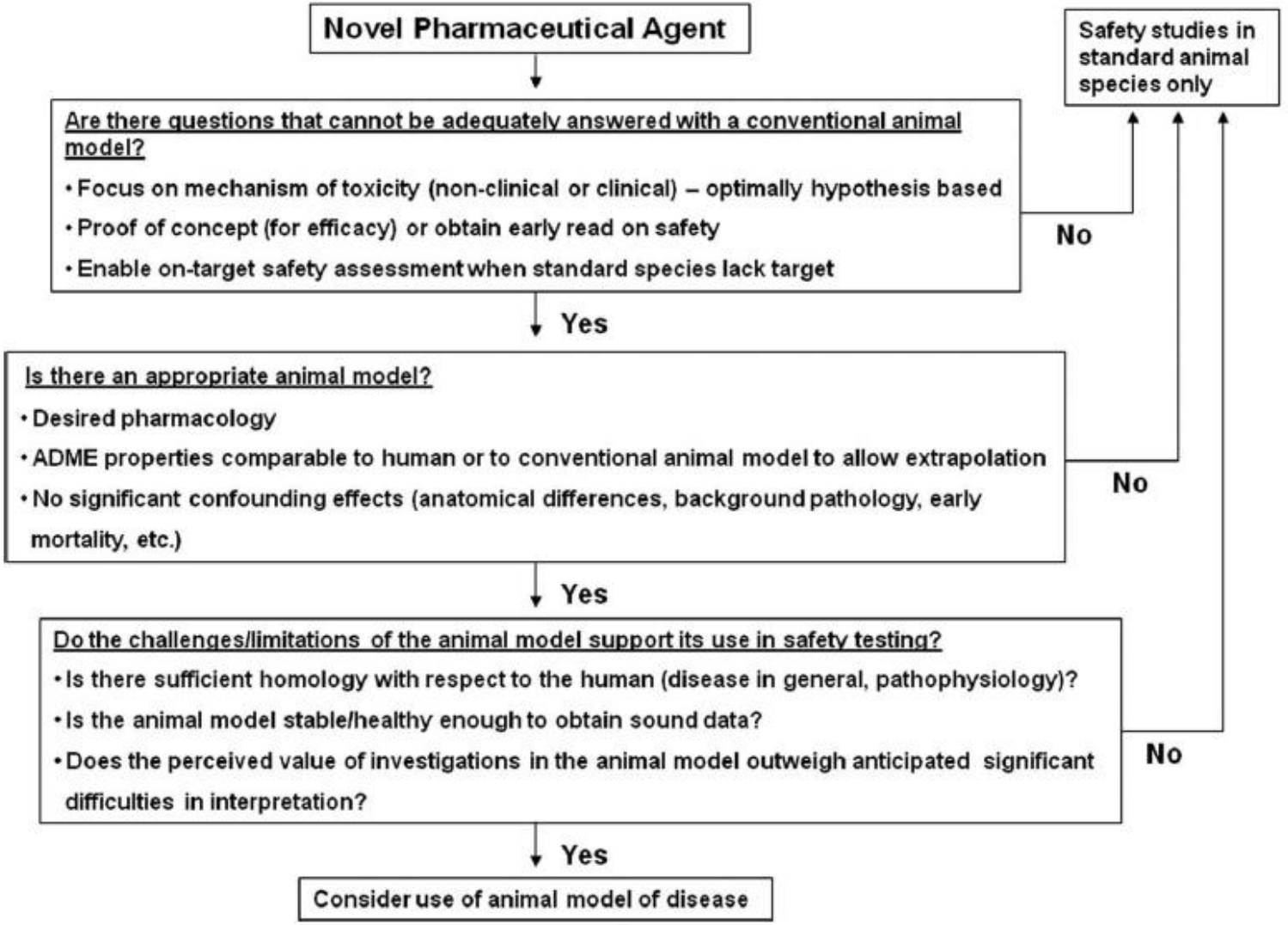
Questions?

Disclosures

- *This presentation was sponsored by AbbVie. AbbVie contributed to the writing, reviewing, and approving the publication. Sherry Morgan is an employee of Abbvie.*

BACKUPS

Use of Animal Model of Disease Consideration: Salient Features



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