

Approaches to TB Drug Development (Past, Present, and Future)

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TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Disclosures

- Dr. Spigelman is a full time employee of the Global Alliance for TB Drug Development

Approaches to TB Drug Development

Past , Present, and Future

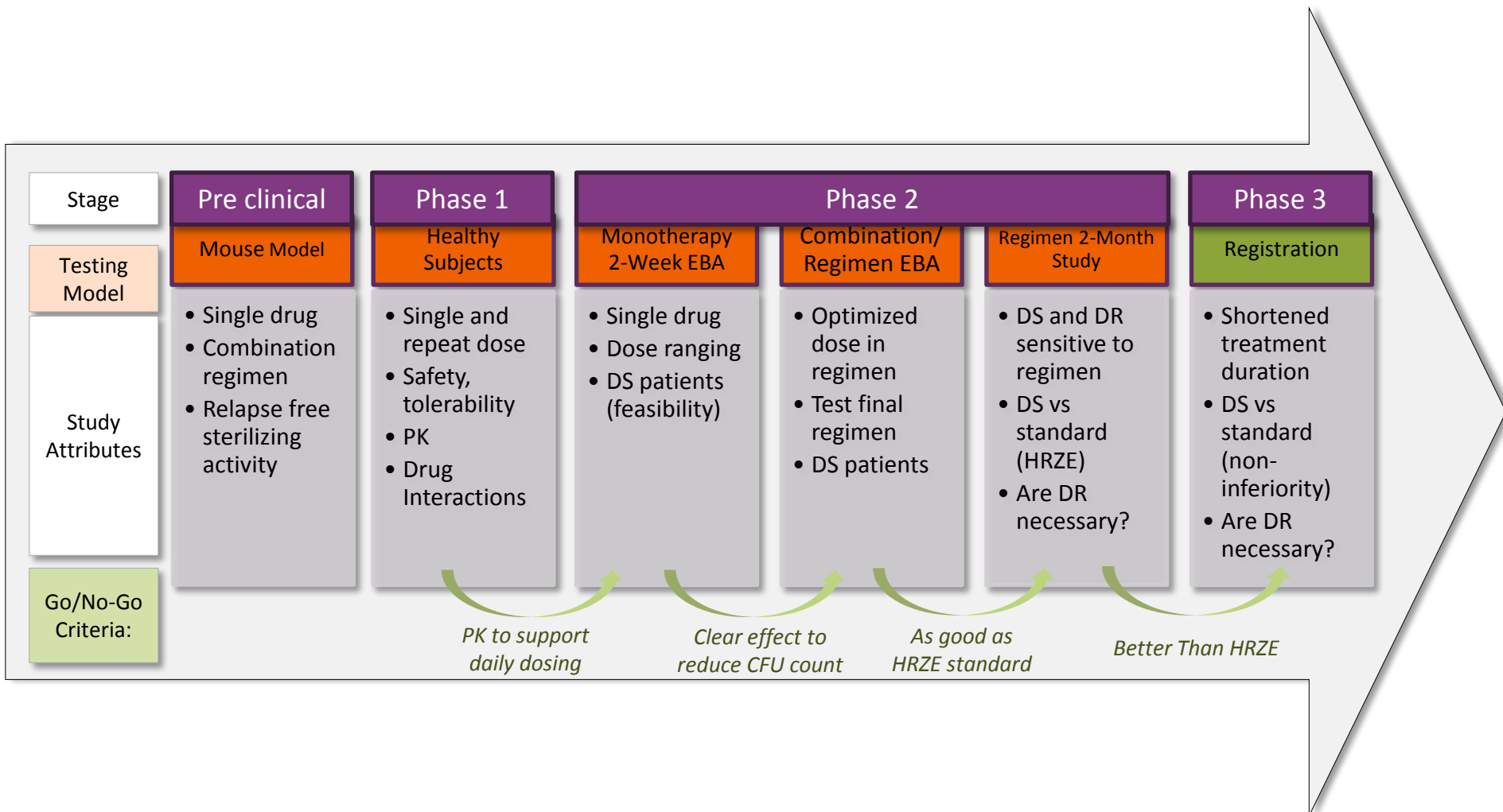
- Ensure explicit clarity on problem being attacked
- Provide practical, cost effective, implementable solution for the identified problem
 - getting a drug approved is necessary, but not sufficient
 - solution does not have to be optimized, but it does have to provide a net compelling benefit to the patient, payer, and health care system
 - would substituting a drug in first line therapy, but not shortening duration, increasing cure, or decreasing side effects provide a net benefit?
 - does adding an additional drug to poor second line regimens to obtain higher sputum conversion rates provide a net benefit?

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Present

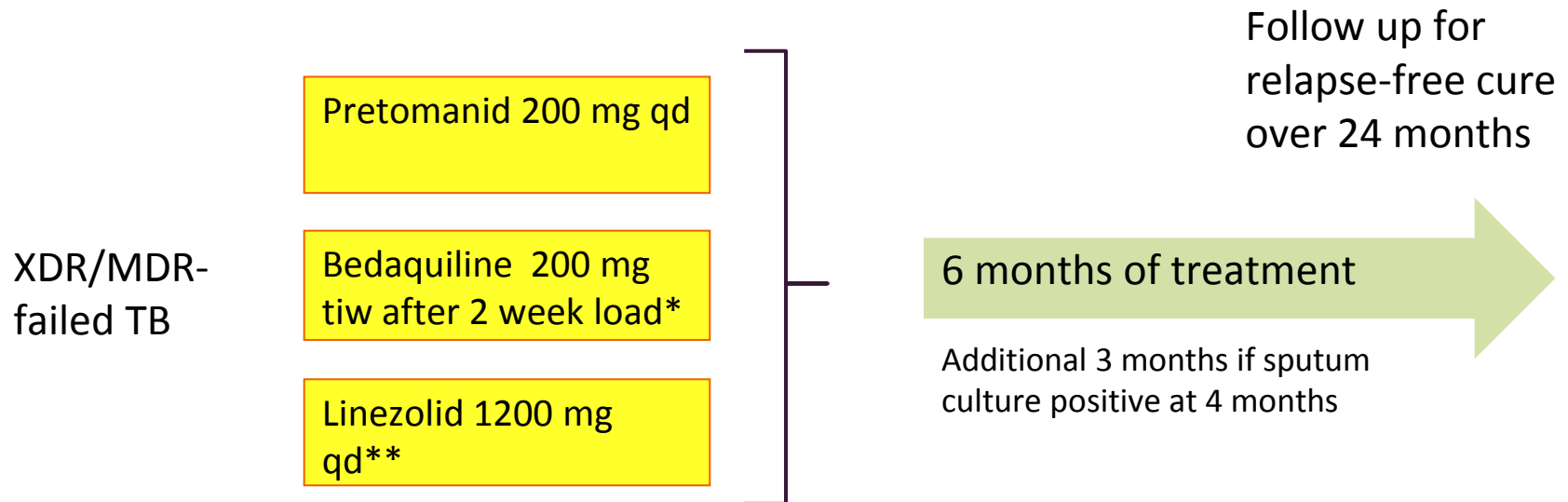
- Unified Pathway – moving forward
- Unified Pathway – moving backwards

Unified Drug Sensitive/Drug Resistant Regimen Development Path



Nix-TB Phase 3 Trial in XDR-TB

Patients with XDR-TB or who have failed or are intolerant to MDR-TB Treatment

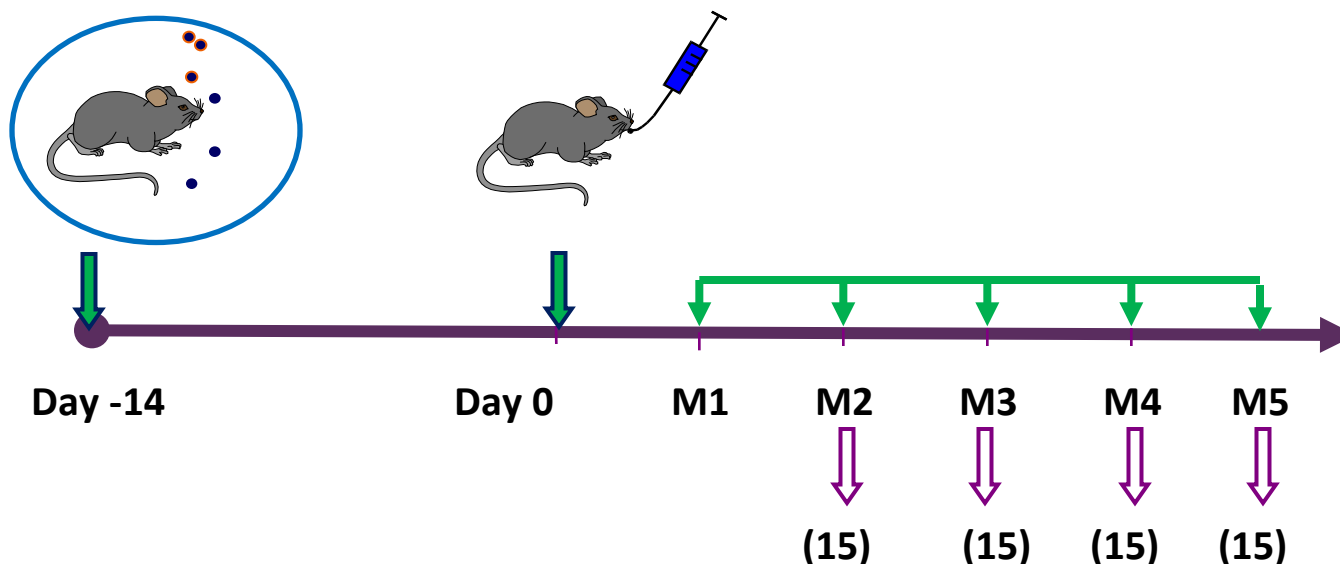


**Amended from
600 mg bid strategy

Major Obstacles to New Approaches

- Lack of “instantaneous” readout of response (degree of TB organisms killed)
 - Severely limits implementation of adaptive designs
- Lack of a predictive quantitative relationship between “Phase 2 readout” (organisms killed) and “Phase 3 readout” (cure)
 - Unclear how to translate culture conversion into duration of therapy for effecting cure
 - Preclinical models, however, are predictive for rank order

Scheme for Mouse Relapse Experiments



(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse

Mouse Relapse Data

	M1.5 (+3)	M2 (+3)	M3 (+3)	M4 (+3)	M5 (+3)
RHZ				10/15	2/15
Pa ₅₀ MZ				6/14	0/14
PaMZ			10/14	3/15	
BPaM			2/15	0/14	
BPaZ	13/14	0/15	0/15		
BPaMZ	3/15	0/15	0/15		

Rank order: BPaMZ > BPaZ > BPaM > PaMZ > RHZ

Future Approaches to TB Drug Development

Without new technological advances

- Large simplified clinical trials
- Multiple arm Phase 3 studies with “large” non-inferiority margins
 - Examine multiple durations of therapy within single trial

Thank You!



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