Lessons Learned in Animal Model Development: Inhalational Anthrax

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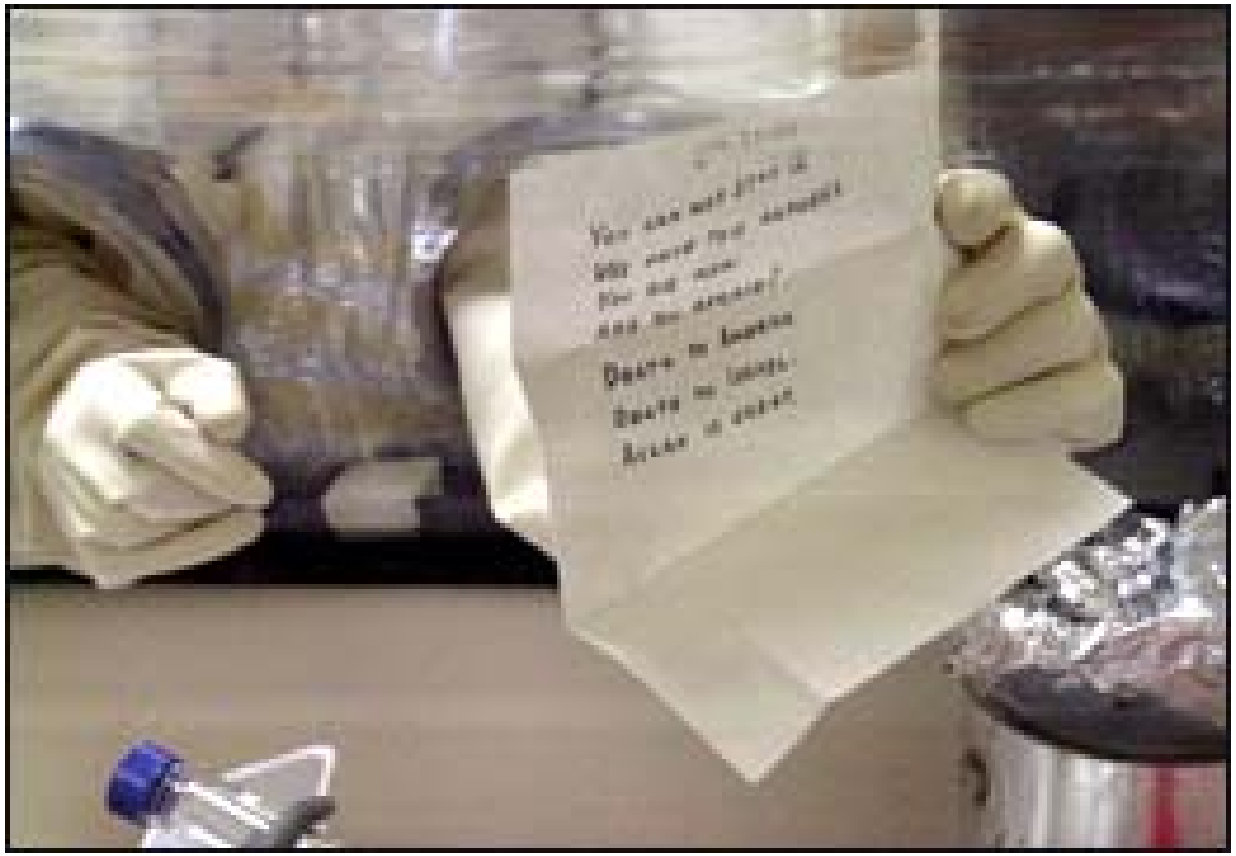
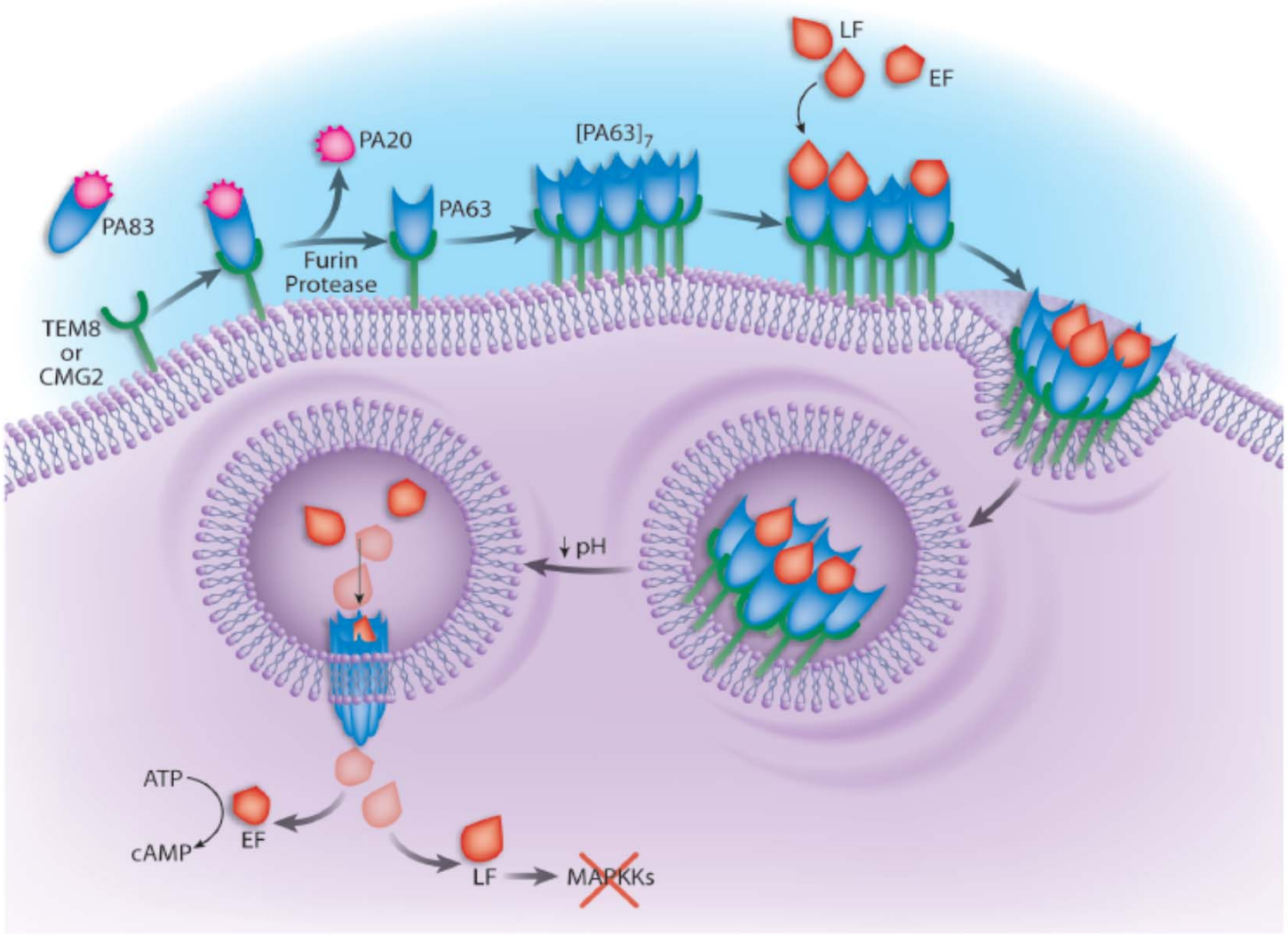


The Unmet Medical Need

- Developing Medical Countermeasures (MCMs) against anthrax
  - Vaccines
    - BioThrax (AVA)
    - rPA
    - Spore coat proteins
  - Antimicrobials
    - Traditional
    - Novel
  - Antibody Passive Protection
    - mAbs
    - Immune globulin
  - Treatment Indication
    - GUP, PEP, Tx

Understanding the Mechanisms of Pathology



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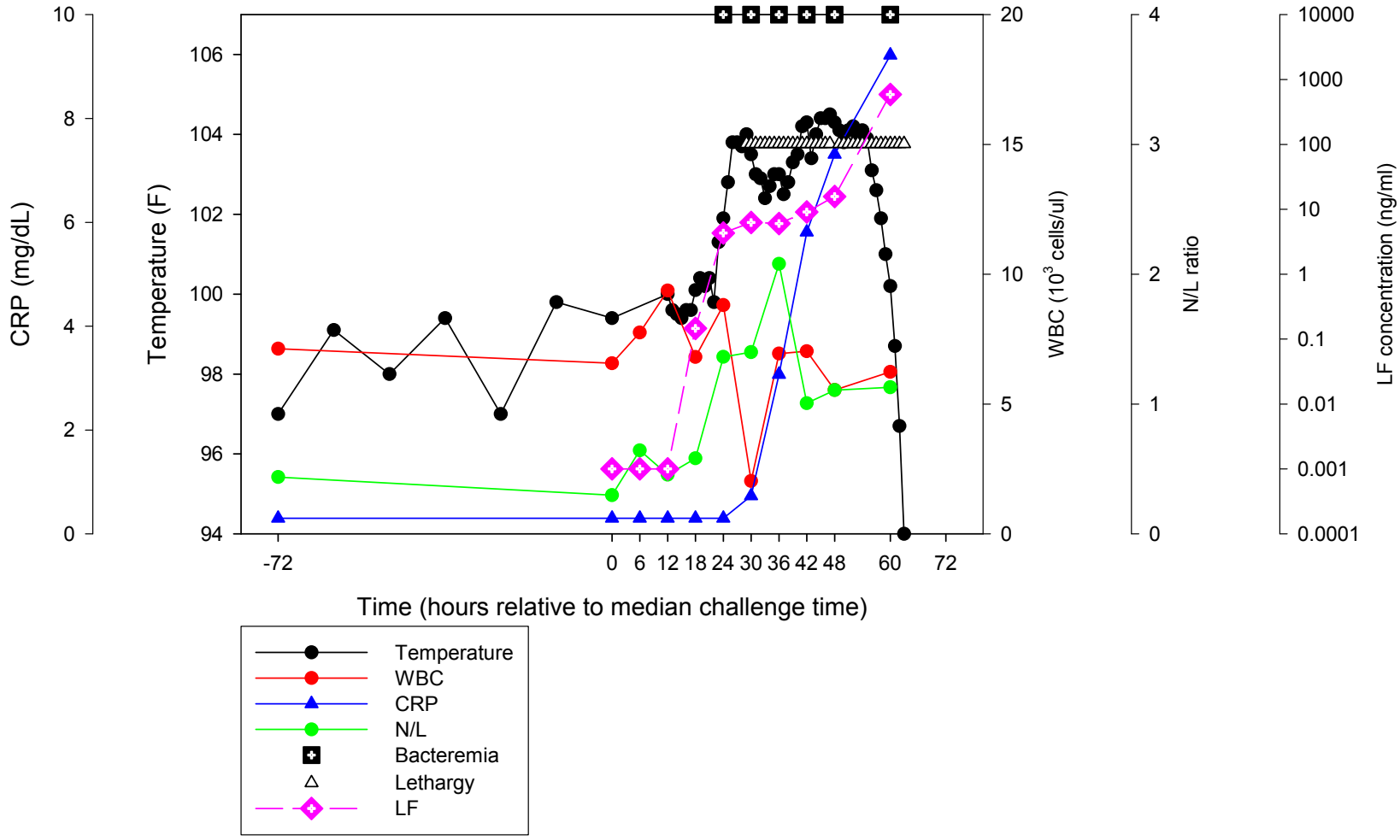
Modeling Therapeutic Treatment (Tx)

Products: Monoclonal Antibodies, Polyclonal Antibodies, Antimicrobial Agents

Requirements:

- Define the disease
  - Clinical signs of illness – non-specific indicators
  - Diagnostics – specific indicators
- Mimic the clinical scenario
  - Clinical presentation
  - Appropriate timing of MCM intervention
  - Our understanding of clinical scenario is based on historical outcomes of Sverdlovsk release in 1979 and 2001 Amerithrax cases

Defining the Disease



Comer et al. Clinical and Vaccine Immunology. 2012 Sep; 19(9) 1517-1525

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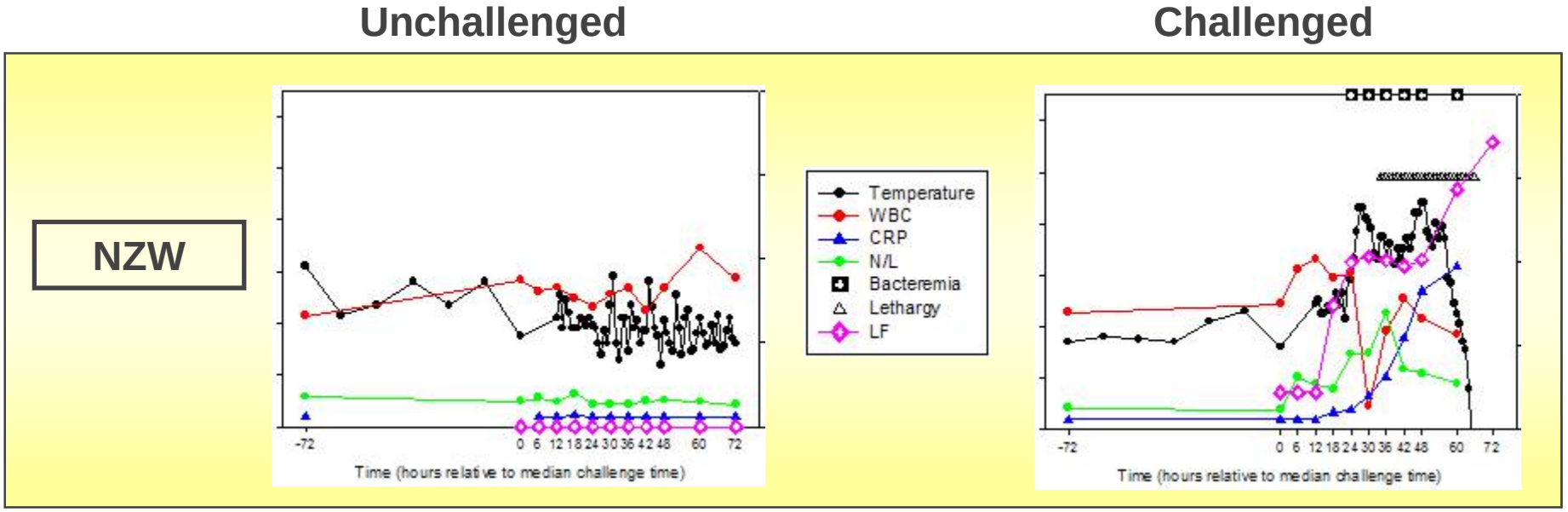
Clinical Profile of Inhalational Anthrax



Next Steps

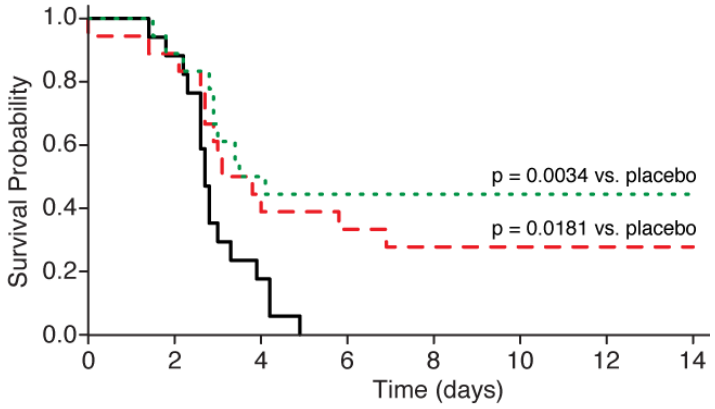
- Demonstrate anthrax antitoxin treatment following confirmation of disease is effective
- Evaluate the PK of antitoxin in the context of the disease

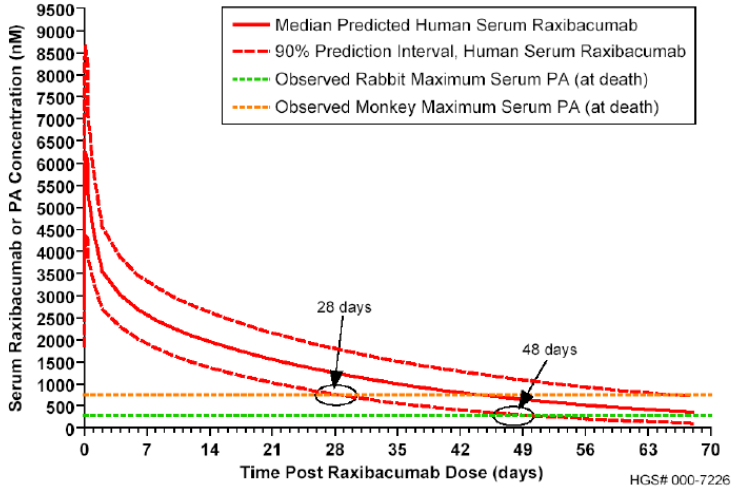
Constraints

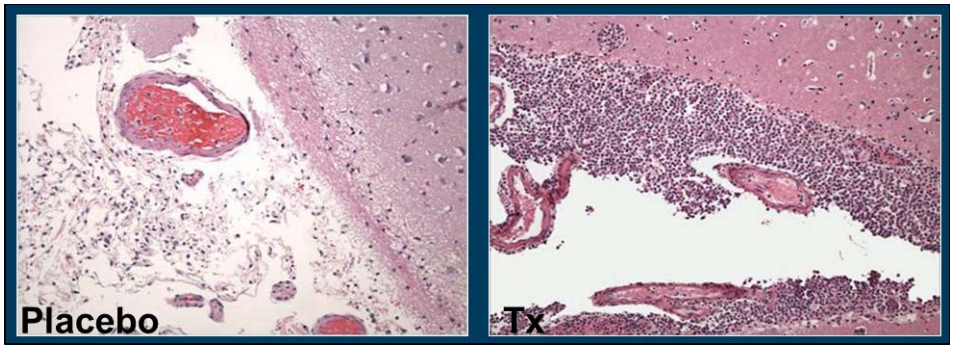
- Traditional diagnosis was impractical – “surrogate” Dx assay was required.
- Limitations in data collection – prioritizing data type was necessary.

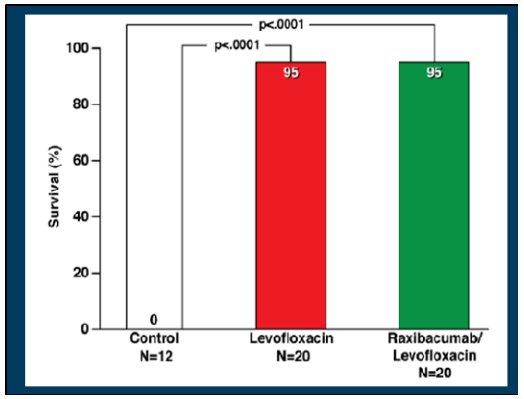
Comer et al. Clinical and Vaccine Immunology. 2012 Sep; 19(9) 1517-1525

Raxibacumab – Demonstrating Effectiveness









www.fda.gov; Migone et al. New England Journal of Medicine. 2009 July 9; 361(2): 135-144

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Clinical Relevance – Added Benefit

Goal

- Demonstrate anthrax antitoxin adds benefit to antimicrobial treatment alone

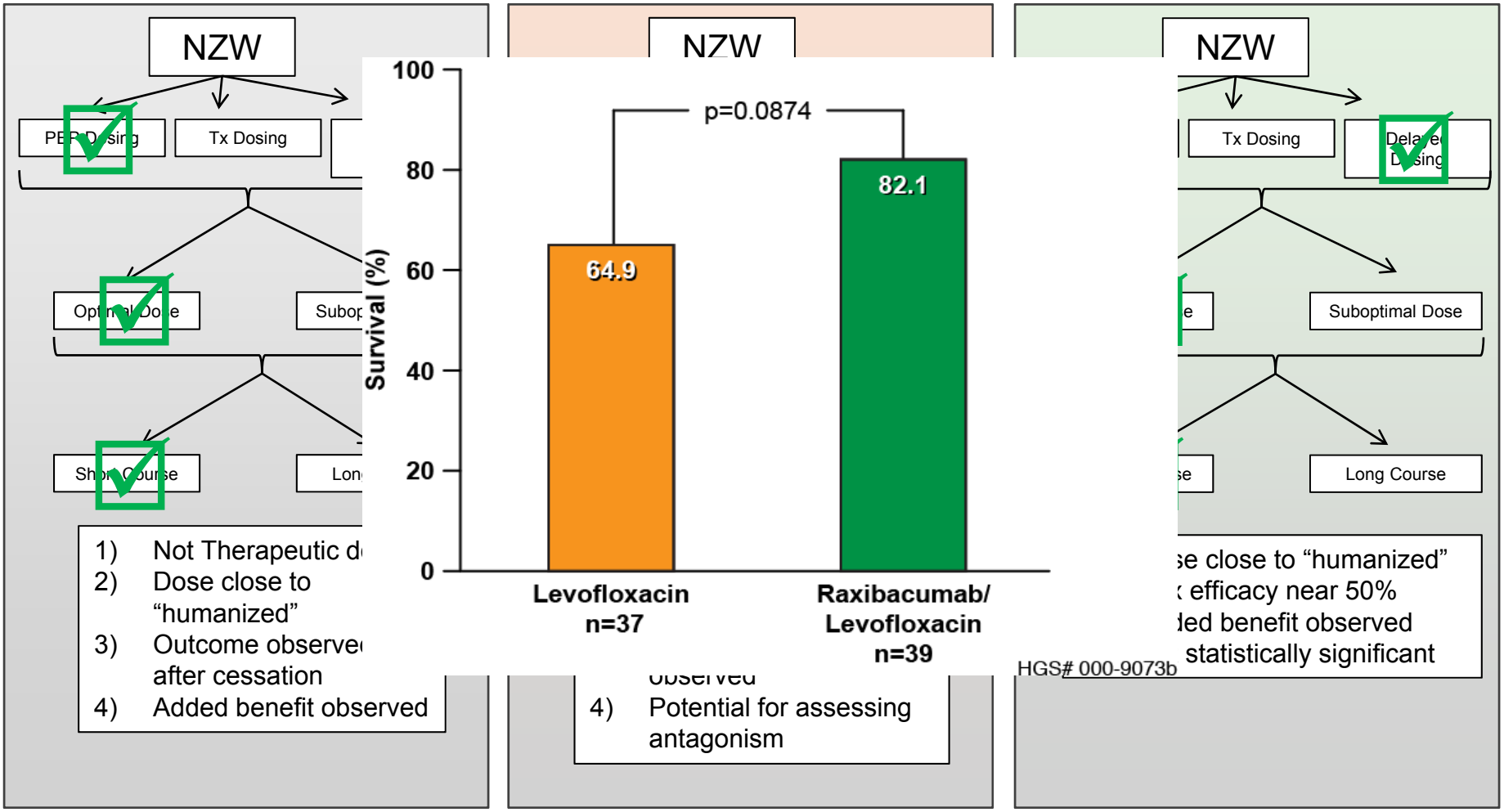
Constraints

- Marginal (~50%) outcome following treatment with antibiotic
- “Humanized” dosing of antibiotic
- Statistically significant difference between outcome observed following treatment with antibiotic and antitoxin when compared to treatment with antibiotic alone

Design Considerations

- Antibiotic dose
- Antibiotic duration
- Treatment intervention time

Clinical Relevance – Added Benefit



www.fda.gov; Corey et al. Toxins 2013, *5*(1), 120-138

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Summary

- Historical data was the foundation of optimizing the models utilized to assess efficacy.
- Indication dictated development pathway.
- Many iterations were required prior to “final” model
- Quality Management System is critical to successful regulatory review
- Collaborative effort was key and critical to the success of the program

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