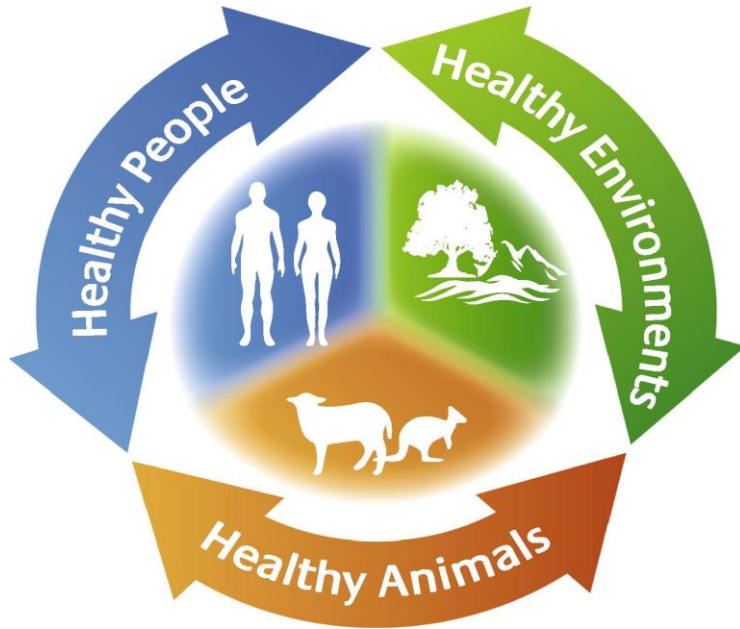


# Antimicrobial Stewardship in Animal Health: Bridging the Valley of Death for Innovative Products

Dr. Jeffrey L. Watts, PhD, RM (NRCM), M (ASCP)  
Research Director, External Innovation  
Zoetis, Kalamazoo, MI

# One Health Principles and the Role of Veterinarians

## The One Health Triad



- The Role of the Veterinarian in One Health
  - Principles embedded in Veterinarian's Oath
    - Protect Animal Welfare
    - Promote Public Health
    - Advance Medical Knowledge
  - Healthy Food Supply
    - Responsible for ensuring that healthy animals enter the food chain
    - Responsible for food inspection
  - Veterinarians impact human health at every meal!

# The Antimicrobial Stewardship Pyramid

Animal Welfare Continuum

Use of the most appropriate agent to protect animal welfare while using the minimal amount of antimicrobial agents

Involvement of Veterinarians to insure proper diagnosis and treatment of disease

Diagnostics for early disease detection and guiding therapeutic choices

Prevention of Disease through Vaccinations, Biosecurity, and Hygiene

# The Perfect Storm of Antimicrobial Resistance



- Emergence of therapy limiting resistance in both human and veterinary medicine
  - ESKAPE Pathogens
    - *Enterococcus (VRE)*, *Staphylococcus (MRSA)*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Enterobacteriaceae (CRE)*
    - “SPACE” Organisms (*Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, *Enterobacter*)
    - Colistin resistance
  - Methicillin-resistant *Staphylococcus pseudintermedius*
  - Multi-Drug resistance *Mannheimia haemolytica* and *Pasteurella multocida*
- Reduced investment in antibacterial discovery
  - Limits substrate availability for veterinary medicine applications

# Animal Health Innovation Imperatives

- Animal Health must develop non-shared classes on novel antibacterials effective in treating animal diseases
  - Avoid or minimize human cross resistance
  - Address both target and human food safety requirements
  - Addresses the four “C”s:
    - Cures (efficacy)
    - Convenience
    - Compliance
    - Cost
- **VETERINARY SPECTRUM SPECIFIC AGENTS**
  - Tune spectrum for treatment of specific animal diseases
    - Bovine Respiratory Disease
    - Canine Pyoderma
  - Tune spectrum to reduce activity against Zoonotic and ESKAPE pathogens

**Driven by Investments  
in the Discovery and  
Development of  
Innovative Products**

# Human and Animal Health R&D Processes



## Human Health Discovery



## Animal Health Discovery

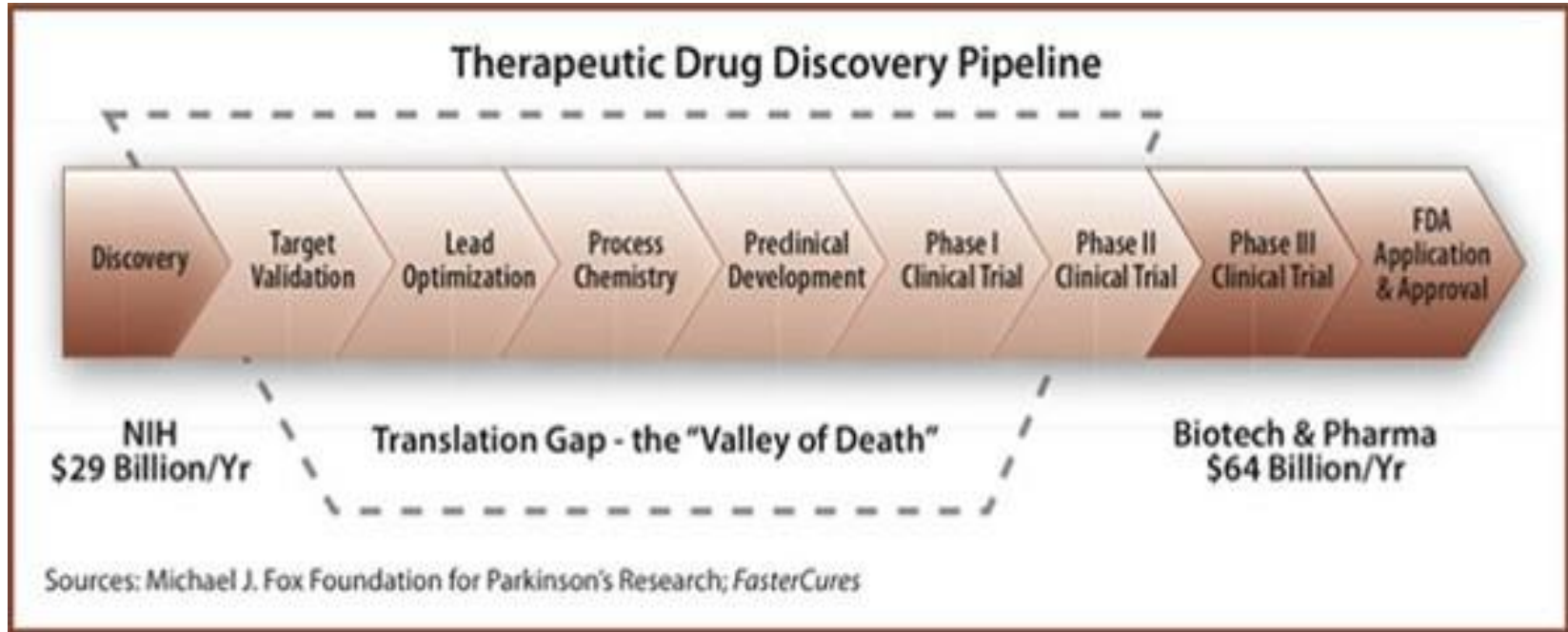
↑ **First in Man Studies**  
(Requires IND or Equivalent)

12–15 years  
800M - 1.5 B

↓ **First Target Animal Studies**  
(Does not require INAD)

8–12 years  
100 – 125 M

# The Valley of Death in Pharmaceutical Discovery



# Substrate Types



## Traditional Small Molecule

- **Novel analogs of existing classes**
  - Ability to tune spectrum to veterinary use is critical
  - Must provide clear separation from agents used in human health
- **Novel Classes**
  - May exploit an existing or novel target
  - Ability to utilize compounds with delivery or safety issues for human health that are not of concern in animal health
  - **Veterinary specific classes**
    - Agents with activity only against veterinary pathogens



# Can We Develop Veterinary Specific Small Molecule Antibacterials?

- **Isoprenoid pathway is essential for synthesis of membrane components**
  - Misic *et al.* used comparative genomics to determine differences in pathways utilized by human and veterinary staphylococci
- **The anti-malarial agent, fosmidomycin, targets the nMEP Pathway**
  - Demonstrated good activity against the canine staphylococci
  - Poor activity against human associated staphylococci
- **Validates the nMEP pathway as a target for a veterinary specific antibacterial**
  - Other templates will likely be needed for development of a useful veterinary antibacterial
    - Requires resource intensive screening and medicinal chemistry programs
- **Compounds with this type of activity would be discarded by HH antibacterial discovery program**
- **The application of genomics may permit the identification of novel targets found only in veterinary pathogens**

# Substrate Types

The header features a solid orange background with a series of white line-art icons of various farm animals including cows, pigs, chickens, and sheep, arranged horizontally across the top.

## Alternatives to Antibiotics (Non-traditional Antibacterials)

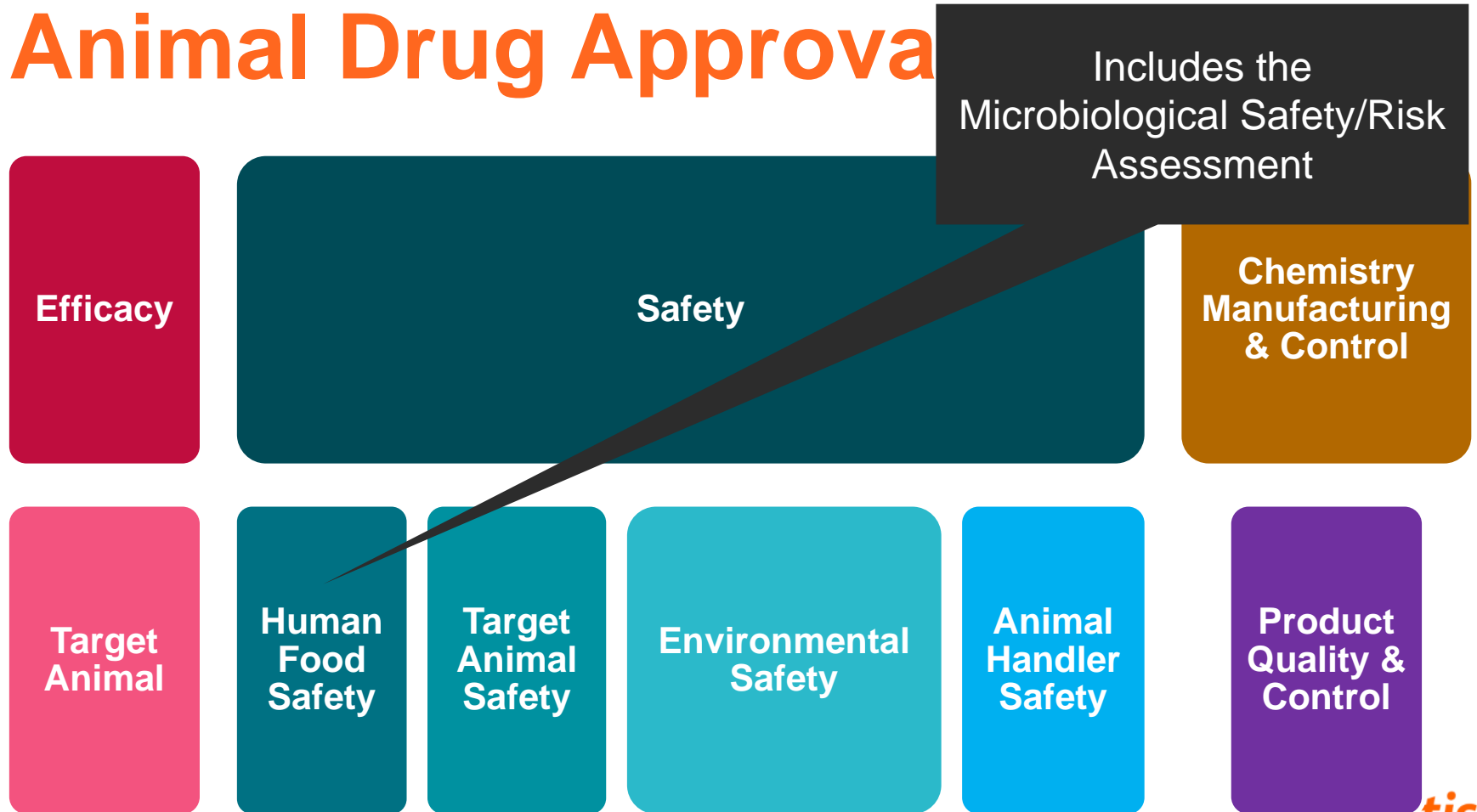
- **Multiple Categories**

- Antimicrobial Peptides
  - Bacteriophages (including Phage Lysin Constructs)
  - Immunomodulators
  - Virulence Modifiers
  - Microbiome (including Probiotics and Competitive Exclusion)
- Each category has a learning curve to understand the appropriate applications and issues associated with that specific substrate
  - Most categories will have applications in the Prevention and Control areas rather than for Treatment

# Regulatory Environment for Alternatives to Antibiotics

- **2012 Alternatives to Antibiotics Meeting**
  - Presentations by both FDA-CVM and EMA
  - Novel Antibacterials not Alternatives to Antibiotics
  - Antibacterial Regulatory Pathway
  - No reductions in efficacy or safety
  - Need to engage early
- **2016 Alternatives to Antibiotics Meeting**
  - FDA/EMA confirmed process 2012 positions
  - Regulatory challenges are not unique to ATA but are shared with all types of innovative technologies
  - Implemented Innovation Teams to foster development of new animal drugs
    - FDA-CVM: Innovation Exploratory Team (IVET) process
    - EMA-CVMP: Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT)

# Animal Drug Approva



# Shepherding Novel Antibacterial Agents Requires Successful Public-Private Partnerships

## University/Startups

- Academic research needs an early focus on product outcomes
- Grant agencies should require an industrial partner for early research proposals
- Understand product characteristics at the time of approval
- Engage a commercial partner early to pipeline entry points
- Entry points can differ between industry partners

## Government

- Provide funding sufficient to support POC studies in target animals
- Require that large human health initiatives include screening of veterinary pathogens

## Industry

- Provide clear guidance on areas of commercial interest and points of entry
- Provide mentorship to university and startups on the development process
- Provide clear understanding of the regulatory requirements and process

# Summary

- **Antimicrobial Stewardship is based upon Prevention through the application of vaccines, hygiene, and biosecurity**
  - Improved diagnostics will play a key role in disease identification and targeted therapeutic applications
- **The introduction of non-shared class, veterinary specific antibacterials will provide the needed therapeutic separation between human and veterinary medicine**
  - The introduction of veterinary specific antibacterials will not reduce the need for antimicrobial stewardship as veterinary medicine will need to preserve the efficacy of these new agents
- **Collaborative public-private partnerships are essential for driving the innovation needed to deliver these novel agents**
- **The Animal Health Industry has a long history of engagement with academic researchers and startups to advance innovative products**

*zoetis*