Challenges in Antibiotic Product Development in a Rapidly Changing Global Landscape

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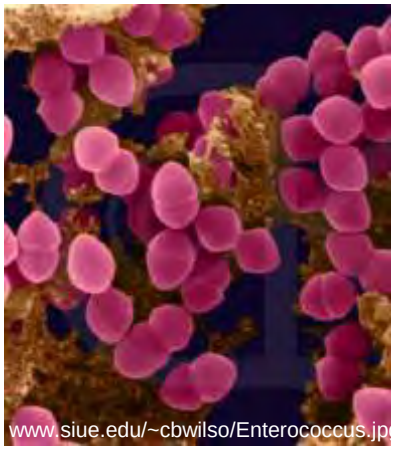
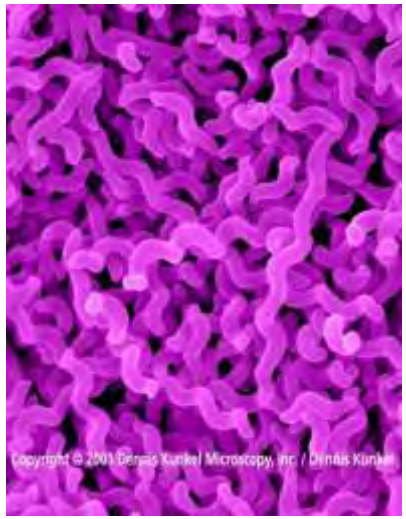
Antibiotic Resistance in Zoonotic Bacteria





- *Salmonella*
- *E. coli*
- *Campylobacter*
- *Enterococcus*

Animal pathogenic bacteria that are targeted by the antibiotic are not the issue

The Challenge

Preserve the efficacy of currently available antimicrobials for use in people and animals.

The challenge

- Strong agreement among experts for balancing “one” global health; the question is:

How can we preserve the efficacy of currently available antimicrobials for use in people and animals?

Basic comments about antibiotic resistance…

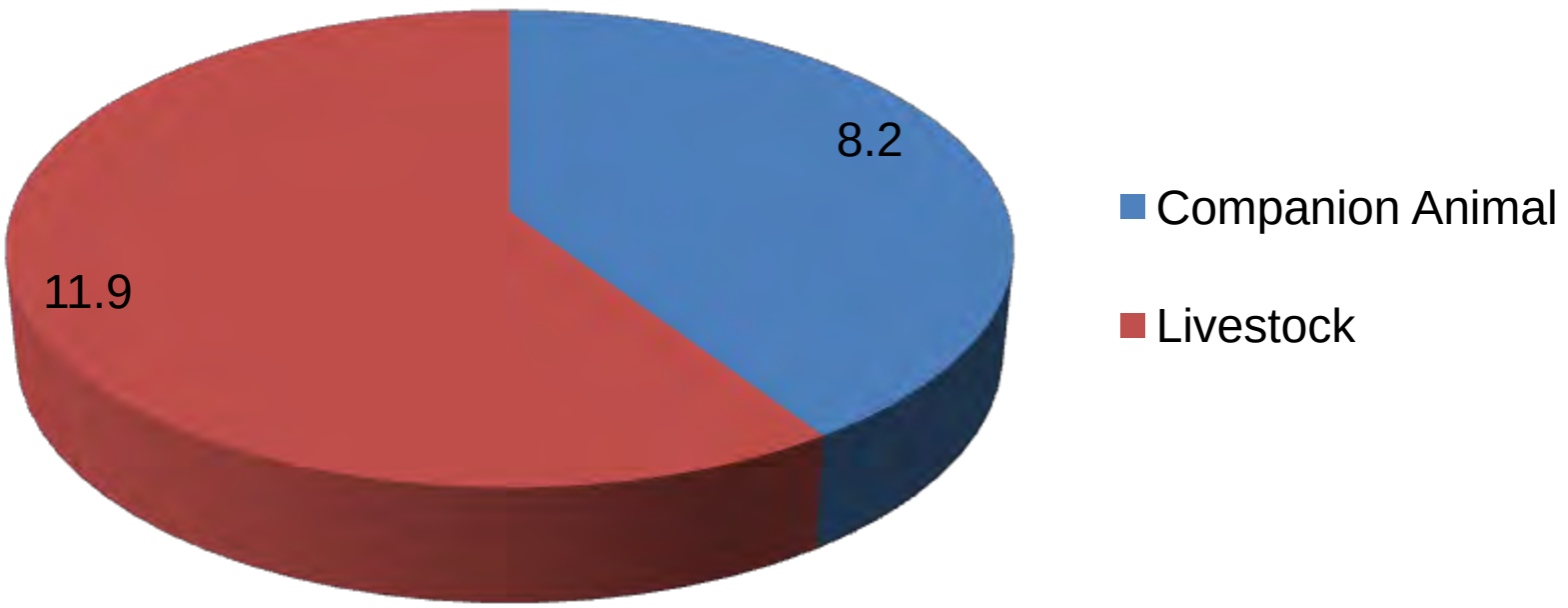
- All antibiotics select for resistance…you look for it in isolation, you can find it
- Antibiotics used in animal health are just like all antibiotics
- Antibiotic resistance poses a risk to human and animal health
- There are many factors that contribute to the emergence and dissemination of antibiotic resistance
  - No one can quantify the “attributable risk” for any one of the complex array of factors that can contribute to ABr

Veterinary Antimicrobials

THE MARKET

Animal Health Industry 2010

Sales (+7.8% nominal growth, +4.0% real growth)



IFAH website, 2011

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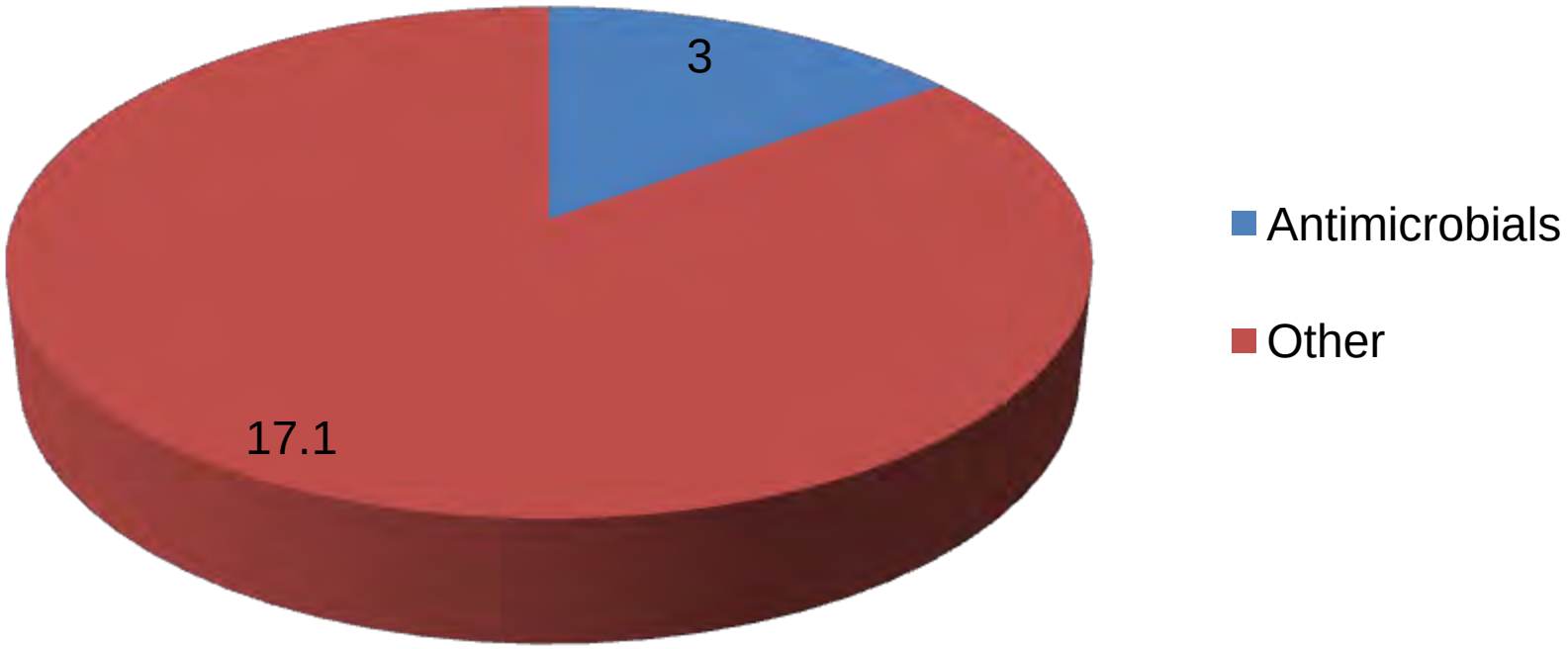
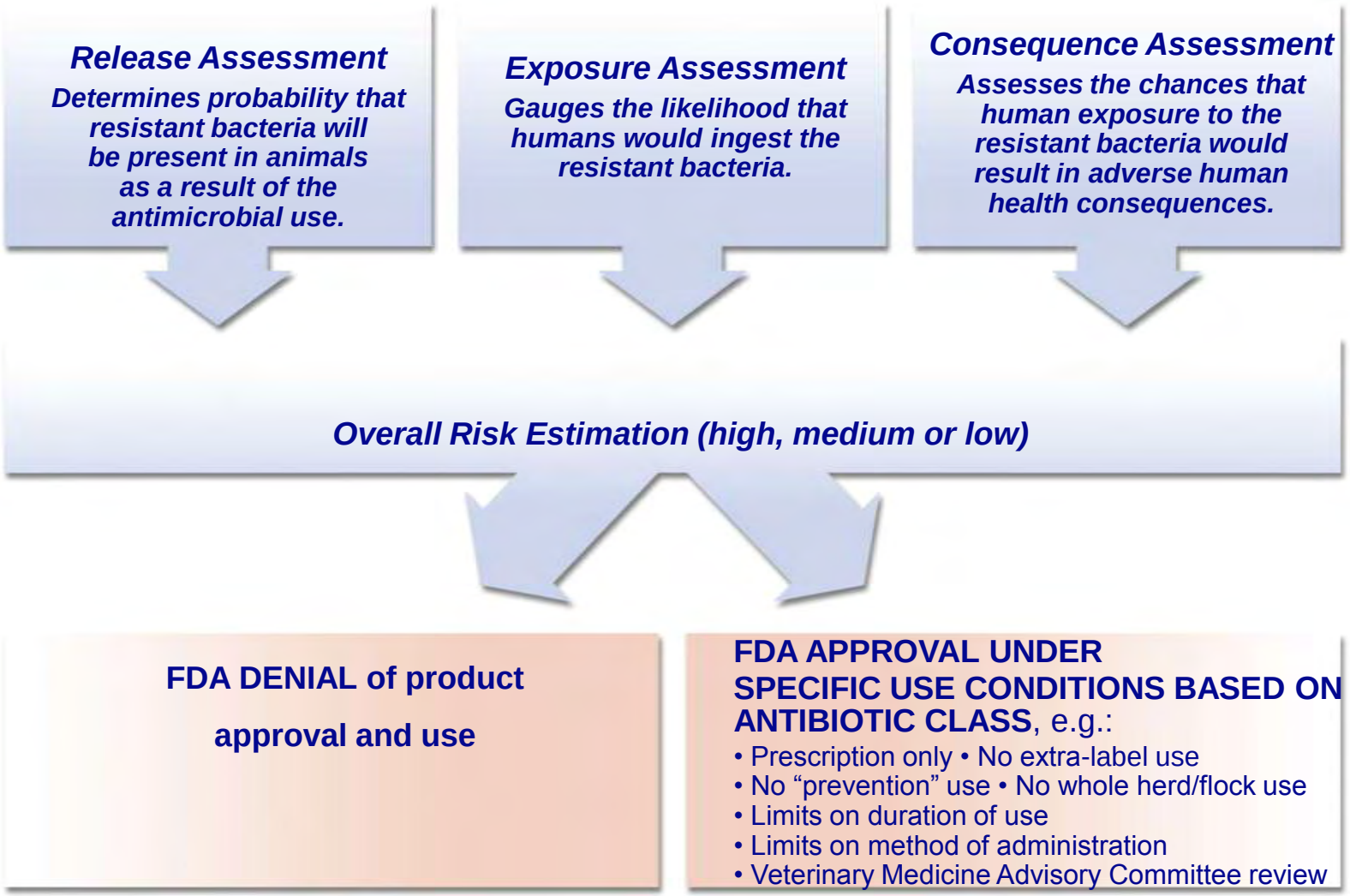


FDA/CVM Guidance #152: Microbial Safety



Precautionary Principle

- Defined in European legislation:
  - The precautionary principle may be invoked where urgent measures are needed in the face of a possible danger to human, animal or plant health, or to protect the environment where scientific data do not permit a complete evaluation of the risk. It may not be used as a pretext for protectionist measures. This principle is applied mainly where there is a danger to public health. For example, it may be used to stop distribution or order withdrawal from the market of products likely to constitute a health hazard.
- A decision to take measures without waiting until all the necessary scientific knowledge is available

Bans on antibiotic growth promoters in feed

Korea: July 2011 (discontinued AB's in feeds)

European Union, 2006

Switzerland, 1999

Denmark, 1998

Sweden, 1986

Government Actions
(withdrawal or limiting of approval)

- US – Baytril water soluble approval revoked by FDA in 2005
- EU - Label restrictions on use as first-line therapy (2011)
  - fluoroquinolones and cephalosporins
- Netherlands (current) – (proposed)
  - To ban all livestock use of beta-lactams, fluoroquinolones, macrolides, lincosaminides in livestock
  - To limit all new antimicrobials to human use
  - To eliminate all in-feed use of antimicrobials
- US – PAMTA (proposed)
  - Eliminates AGP, prevention and control claims for premix and water soluble products with critical antimicrobial animal drugs – unless Health and Human Services Secretary determines safety
  - Defines "critical antimicrobial animal drug" as one that is: "(1) intended for use in food-producing animals; and (2) is composed wholly or partly of—(A) any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide; or (B) any other drug or derivative of a drug that is used in humans or intended for use in humans to treat or prevent disease or infection caused by microorganisms."
- US – Extra-label Drug Use restrictions/prohibitions (proposed)
- US – Elimination of growth promotion indications for medically important ABs (proposed)

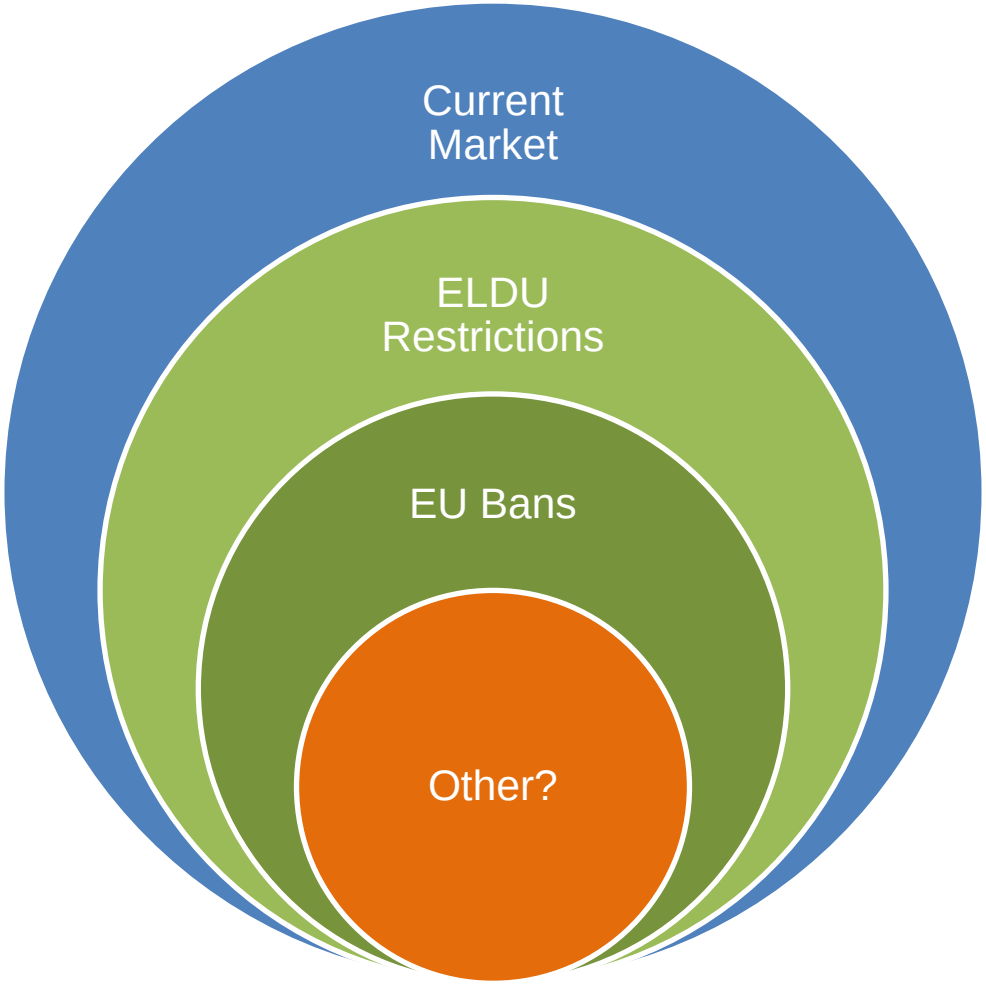
EU likely to expand focus

- Incoming EU president from Denmark, 2012
- Antibiotic resistance a priority
- Interest in a common EU surveillance program for antibiotic consumption and antimicrobial resistance
- Goal to reduce antibiotic consumption among both humans and animals with focus on the critically important antibiotics
- Potential incentives for R&D to expand available options

Other Market Limiting Factors

- A preference for holding new products “in reserve” in the expectation that they will not be overused and subsequently lose their effectiveness due to resistance emergence
- Formularies that serve to direct veterinarians in which products to use or avoid; based in part on human importance ranking lists

Antimicrobials Marketplace… Where is it going?

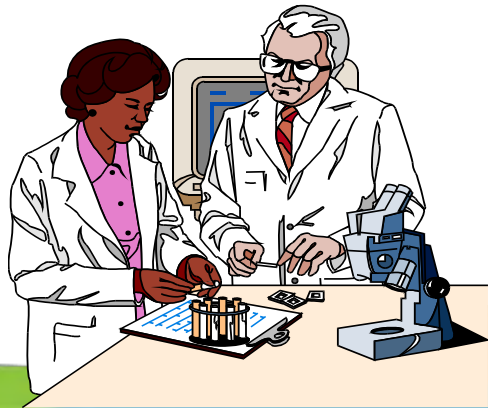


Veterinary Antimicrobials

THE REGULATORY PROCESS

Veterinary Drug Discovery

- 10+ years and $100 million investment
  - Quality, safety (human and animal) and effectiveness
- Global animal health anti-infectives market
  - Approximately $3 billion dollars in 2008
- Industry consolidation means less internal antibiotic expertise available, similar to human pharma
  - Most current "new vet antibiotics" discovered in 1980s
  - Most came from Human Discovery programs
  - Now seeking external opportunities
- Internal business competition of antibiotic opportunities vs. non-antibiotic candidates
  - Return on investment for shareholders
  - Probability of technical and regulatory success
  - External stakeholder issues



Large US and European Pharmaceutical Companies Conducting Antibacterial Research

1980 (N=36)

- Abbott
- Astra
- Ayerst
- Bayer
- Beecham
- Bristol-Myers
- Burroughs
- Ciba-Geigy
- Dow
- DuPont
- Glaxo
- Hoechst
- ICI
- Lederle
- Lilly
- Marion
- Merck
- Merrell
- Miles
- Parke Davis
- Pfizer
- Pharmacia
- Proctor & Gamble
- Rhone-Poulenc
- Rorer
- Roche
- Roussel
- Sandoz
- Sanofi
- Schering
- SmithKline
- Squibb
- Upjohn
- Warner-Lambert
- Wellcome
- Wyeth

1998 (N=20)

- Abbott
- Astra
- Bayer
- Bristol-Myers Squibb
- Glaxo Wellcome
- Hoechst Marion Roussel
- Johnson & Johnson
- Lilly
- Merck
- Novartis
- Parke Davis
- Pfizer
- Pharmacia & Upjohn
- Rhone-Poulenc Rorer
- Roche
- Sanofi
- Schering
- SmithKline Beecham
- Wyeth-Ayerst
- Zeneca

2010 (N=3 to 7)*

- AstraZeneca
- (Glaxo SmithKline)
- (Johnson & Johnson)
- (Merck-Schering Plough)
- Novartis
- (Pfizer -Wyeth)
- Sanofi-Aventis

*( ) = diminished effort

Slide courtesy KA Bush, Indiana University

Slowing pipeline...

Table 1 | **Recently approved antibiotic products for animals**

Antibiotic	Class	Drug sponsor	Year of approval	Species	Indications
Enrofloxacin	Fluoroquinolone	Bayer	1987	Cattle, poultry, pets	Respiratory disease
Ceftiofur	Third-generation cephalosporin	Pfizer	1988	Cattle, swine	Respiratory disease
Tilmicosin	Macrolide	Elanco	1990	Cattle	Respiratory disease
Florfenicol	Phenicol	Schering–Plough	1991	Cattle, swine, aquaculture	Respiratory disease
Danofloxacin	Fluoroquinolone	Pfizer	1991	Cattle	Respiratory disease
Cefquinome	Fourth-generation cephalosporin	Intervet	1995	Cattle	Respiratory disease
Marbofloxacin	Fluoroquinolone	Vetoquinol	1995	Dogs, cats, cattle	Skin, urinary and respiratory disease
Orbifloxacin	Fluoroquinolone	Schering–Plough	1997	Dogs, cats	Skin and urinary disease
Difloxacin	Fluoroquinolone	Fort Dodge	1998	Dogs, chickens	Skin and respiratory disease
Valnemulin	Pleuromutilin	Novartis	1998	Swine	Respiratory disease
Ibafloxacin	Fluoroquinolone	Intervet	2000	Dogs	Skin and urinary disease
Tulathromycin	Macrolide	Pfizer	2003	Cattle, swine	Respiratory disease

Since 2004…Tylvalosin, gamithromycin , tildipirosin

Shryock, 2004. Nature Reviews - Microbiology

Major Classes of Antimicrobials (shared human use classes)

β-lactams	Penicillin, amoxicillin; ceftiofur
Macrolides & lincosamides	Tylosin; tilmicosin; tulathromycin, lincomycin
Aminoglycosides	Gentamicin; neomycin
Fluoroquinolones	Enrofloxacin, danofloxacin
Tetracyclines	Tetracycline; oxytetracycline, chortetracycline
Sulfonamides	Various
Streptogramins	Virginiamycin
Polypeptides	Bacitracin
Phenicols	Florfenicol
Pleuromutilin	Tiamulin

Why people & animals share antibiotic classes

- Pathogens are similar in people and animals
- R&D-driven for humans; animals secondary (yet important) beneficiaries

Potential risks cited for “sharing”	Potential risks cited for not “sharing”
Resistance development, with human health implications	Animal mortality
Residues in meat/milk from improper use	Disease outbreaks, with animal and human health risks
	Illegal and off-label use

WHO CIA List criteria

2.2 The WHO list of critically important antimicrobials

The WHO list of critically important antimicrobials was based on the following criteria for categorization as developed by two Expert Meetings (WHO, 2005; WHO, 2007):

- **Criterion 1** Sole therapy or one of few alternatives to treat serious human disease.
- **Criterion 2** Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

The definitions of the different categories were as follows:

Critically important antimicrobials are those that meet criteria 1 and 2

Highly important antimicrobials are those that meet criteria 1 or 2

Important antimicrobials are those that meet neither criteria 1 nor 2

FAO/WHO/OIE. 2008. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials. Report of a meeting held in FAO, Rome, Italy, 26–30 November 2007. FAO, Rome, Italy, and WHO, Geneva, Switzerland.

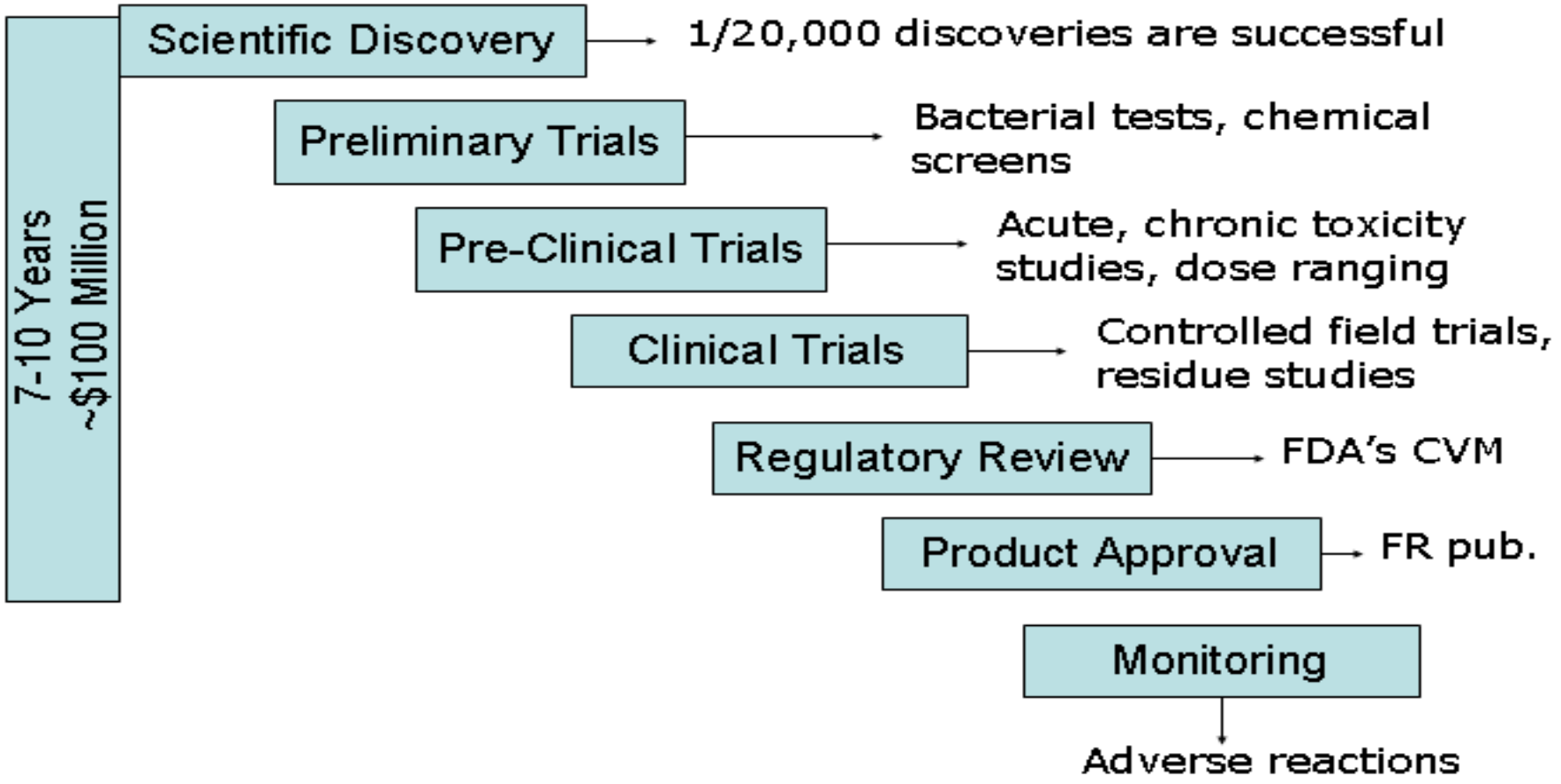
Joint Consultation, Rome, 2008

Table 4. Comparison of the human clinically important antimicrobials and veterinary clinically important antimicrobials lists

Critically important antimicrobials used in human medicine	Veterinary critically important antimicrobials
Aminoglycosides	Aminoglycosides
Cephalosporins (3rd and 4th generation)	Cephalosporins
Macrolides	Macrolides
Penicillins (natural, aminopenicillins and antipseudomonal)	Penicillins
Quinolones	Quinolones
Tetracyclines (only tigecycline)	Tetracyclines
Ansamycins	
Carbapenems	
Glycopeptides	
Oxazolidinones	
Streptogramins	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	
	Phenicols
	Sulfonamides

FAO/WHO/OIE. 2008. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials. Report of a meeting held in FAO, Rome, Italy, 26–30 November 2007. FAO, Rome, Italy, and WHO, Geneva, Switzerland.

Discovery, Approval and Post Approval



What Might a New Antibiotic Look Like?

- Non-human antimicrobial class (or unique analog) is preferred to avoid cross-resistance with human use
  - Low potential for later development for human use
- Narrow spectrum agent vs. broad spectrum
- A bactericidal mechanism is preferred to a bacteriostatic mechanism to minimize co-resistance and cross-resistance selection
- Parenteral route of administration is preferred when possible, oral (water and feed) medications are acceptable for group treatment when injectable products are not feasible (e.g. poultry or swine)
- Appropriate label directions to guide end-user in use of the product to ensure minimal (or no) food borne bacteria resistance selection

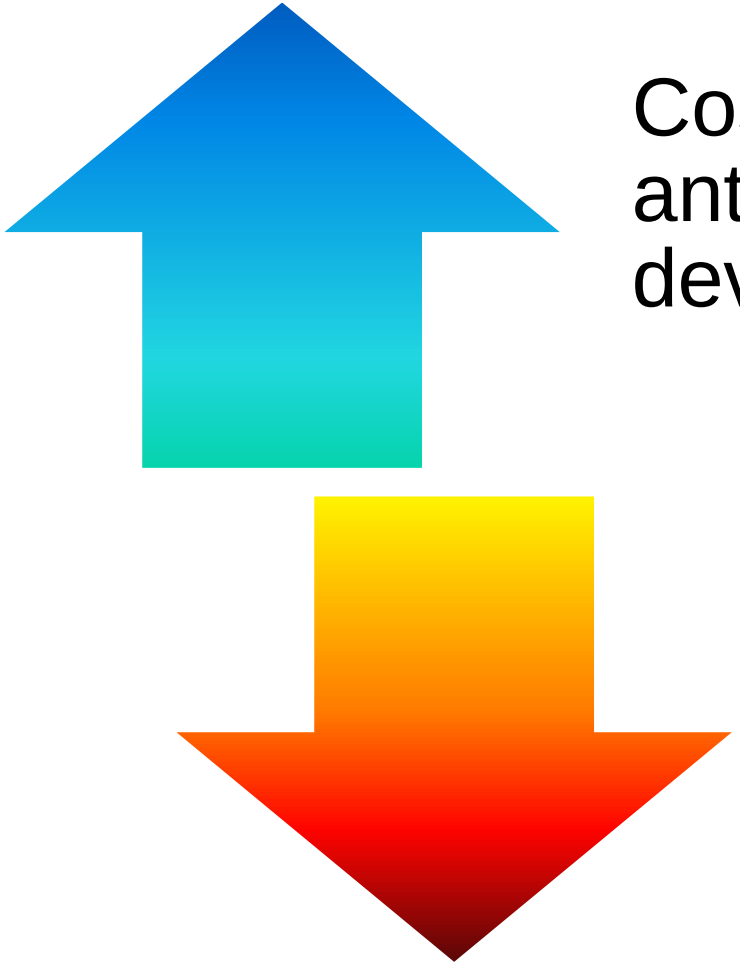
Other Features to Support New Products…

- The need for antimicrobial susceptibility testing methods and clinical breakpoints to enable laboratory testing results to guide the selection of an appropriate product by a vet
  - CLSI clinical breakpoints
- Adequate diagnostic methods to ensure that the clinical disease is associated with a pathogen that could be treated with an antimicrobial agent for targeted therapy (e.g. it is a bacterial and not a viral infection)
  - “Quick tests” done on-site vs. traditional laboratory tests
- Off-label use restrictions

Veterinary Antimicrobials

THE CONSEQUENCES

The Product Development Dilemma



Cost and time of antibiotic product development

Size of the antimicrobials markets as bans and restrictions are implemented

Consequences of Restrictions and Prohibitions

Intended Consequences?

- Precious antibiotics saved for use in humans only
- Alleged reduction in selective pressure for medically important antibiotics
- Alleged reduction in selective pressure for MDR plasmids and pathogens

Unintended consequences?

- Widespread off-label and/or illegal use
- Intense use of a very few classes of antibiotics
- Major animal diseases left untreated or untreatable
- Increase in animal morbidity and mortality
- Human health/food safety jeopardized
- Reduced incentive to develop new antimicrobials

Competing Innovation for the Future

- Novel non-antibiotic interventions…
  - Immunomodulatory compounds
  - Phage therapy or carcass treatment
  - Non-antibiotic performance products
  - Microorganism-based products (probiotics)
  - Nutraceuticals
  - Vaccines (live, attenuated, killed, subunit)
  - Virulence or quorum blockers
  - Disease-resistant animal breeds
  - Other approaches?

Incentives for New Antibiotics for Human Use

- Extended patent life or regulatory exclusivity
- Research credit for antibiotic investment
- Public-Private partnerships
- Pricing considerations to fund new research

- Will or should these incentives include animal use antibiotics?

Wouldn't it also be great if…

- One Health Initiative was considered
  - A movement to forge co-equal, all inclusive collaborations between physicians, veterinarians, and other scientific-health related disciplines
  - http://www.onehealthinitiative.com/
- Researchers who discovered novel anti-infective compounds also considered the potential for animal health product development?
- Collaborations to find the best ways to use antibiotics were fostered between the medical and veterinary sectors?

Summary

- Antibiotics are the only product category where increase use theoretically promotes more rapid obsolescence
- The changing global landscape of antibiotic use restrictions has undermined the value of new product development
- The speed of change of the regulatory and political landscapes is faster than product development can move
- The results of these actions will reduce the ability of veterinarians to treat and control animal diseases over the next 10-15 years

Challenges in Antibiotic Product Development in a Rapidly Changing Global Landscape

QUESTIONS?