Global Perspectives of Antimicrobial Resistance

Scott A Brown, DVM, PhD, DACVCP
Pfizer Animal Health
representing IFAH

Who is IFAH?

International Federation for Animal Health - IFAH

The International Federation for Animal Health (IFAH) is the global representative body of companies engaged in research, development, manufacturing and commercialization of veterinary medicines, vaccines and other animal health products in both developed and developing countries across the five continents.
Corporate members

- ALPHARMA  
  Animal Health

- Bayer HealthCare  
  International Animal Health

- Boehringer Ingelheim  

- Elanco

- Lohmann  
  Animal Health

- Pfizer  
  Animal Health

- Vétoquinol  
  Sante de l’animal

Member associations
## Member associations

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Why does IFAH exist?

The mission of IFAH is
- to foster a greater understanding of animal health matters and
- to promote a predictable, science-based regulatory environment that facilitates the supply of innovative and quality animal medicines, vaccines and other animal health products into a competitive market place.

These products contribute to the health and welfare of animals and importantly provide a safe food supply for people.

General objectives and goals
- To achieve a balanced regulatory and trade framework that fosters innovation while recognising the social and political environment;
- To encourage constructive dialogue with governments, public policy makers, legislators, regulators, the veterinary profession, the food chain, consumers and other stakeholders;
- To ensure that the contribution of the animal health industry to health and quality of animal and human life through the advancement of sound science is understood by society at large.
Food Economics and Consumer Choice

An overview of the challenge ahead

Key Data

- In 50 years, the world population will require 100% more food, and 70% of this food must come from efficiency-improving technology.


Antibiotic Resistance in Zoonotic Bacteria

- Salmonella
- E. coli
- Campylobacter
- Enterococcus

Animal pathogenic bacteria that are targeted by the antibiotic are not the issue.
It’s a complex issue, often incorrectly simplified, thus misleading to the public

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?
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

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<th>Novartis</th>
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<td>(Johnson &amp; Johnson)</td>
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<td>(Merck-Schering Plough)</td>
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*[] = diminished effort

Slide courtesy KA Bush, Indiana University
Major Classes of Antimicrobials
(shared human use classes)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>β-lactams</td>
<td>Penicillin, amoxicillin, ceftiofur</td>
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<tr>
<td>Macrolides &amp; lincosamides</td>
<td>Tylosin, tilmicosin, tulathromycin, lincomycin</td>
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<tr>
<td>Aminoglycosides</td>
<td>Gentamicin, neomycin</td>
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<tr>
<td>Fluoroquinolones</td>
<td>Enrofloxacin, danofloxacin</td>
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<tr>
<td>Tetracyclines</td>
<td>Tetracycline, oxytetracycline, chortetracycline</td>
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<tr>
<td>Sulfonamides</td>
<td>Various</td>
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<td>Streptogramins</td>
<td>Virginiamycin</td>
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<td>Polypeptides</td>
<td>Bacitracin</td>
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<tr>
<td>Phenicols</td>
<td>Florfenicol</td>
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<tr>
<td>Pleuromutilin</td>
<td>Tiamulin</td>
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Why people & animals share antibiotic classes

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

<table>
<thead>
<tr>
<th>Potential risks cited for “sharing”</th>
<th>Potential risks cited for not “sharing”</th>
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<tr>
<td>Resistance development, with human health implications</td>
<td>Animal mortality</td>
</tr>
<tr>
<td>Residues in meat/milk from improper use</td>
<td>Disease outbreaks, with animal and human health risks</td>
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<td>Illegal and off-label use</td>
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Global Reports on Animal Antibiotic Use since 1997

- WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture, AGISAR)
- OIE Terrestrial Code
- Codex—various (TFAMR)
- Europe (CVMP, EFSA, ECDC; EU commission)
- Australia (JETACAR)
- U.S. (NRC, CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
- Canada (Adv. Com. Report, CCAR)
- Other reports from APUA, IFT, Pew

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 (WIIO, 2005; WIIO, 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 caused 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

Joint Consultation, Rome, 2008

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

<table>
<thead>
<tr>
<th>Critically important antimicrobials used in human medicine</th>
<th>Veterinary critically important antimicrobials</th>
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<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
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<tr>
<td>Cephalosporins (3rd and 4th generation)</td>
<td>Cephalosporins</td>
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<tr>
<td>Macrolides</td>
<td>Macrolides</td>
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<tr>
<td>Penicillins (natural, amoxicillin and antipseudomonal)</td>
<td>Penicillins</td>
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<tr>
<td>Quinolones</td>
<td>Quinolones</td>
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<tr>
<td>Tetracyclines (only tigecycline)</td>
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<td>Ansamycins</td>
<td>Phenicols</td>
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<td>Sulfonamides</td>
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<td>Glycopeptides</td>
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<td>Oxazolidinones</td>
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<td>Streptogramins</td>
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Drugs used solely to treat tuberculosis or other mycobacterial diseases


Antibiotic Uses

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<th>Efficacy</th>
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<td>Disease Treatment</td>
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- **Disease treatment**
  - Therapeutic
- **Disease control**
  - Therapeutic
- **Disease prevention**
  - Therapeutic
- **Performance or “Growth promotion”**
Key Messages

- Risk analysis is product and indication specific
  - all antibiotics are not created equal
- Monitoring / surveillance of resistance trends are important
  - respond to relevant data, not perceptions
- Responsible use by veterinarians is a primary risk mitigator
  - animals get sick and need medicines, just like people

Risk Analysis
Risk Assessment Recommendations

- WHO Responsible Use Guidelines (# 18 and 19)
- OIE Terrestrial Code (Chapter 6.11)
- Codex GL61 on Responsible Use
- Codex Task Force on Antimicrobial Resistance
- US Public Health Action Plan (#49-51)
- US Regulatory risk assessment G152
Risk Analysis Components

Comparison of Qualitative and Quantitative Risk Assessments

Qualitative Risk Assessments
- Easier to understand
- Require less quantitative data
- Provide categorical assessments (based on predefined terms and criteria)

Quantitative Risk Assessment
- More complex, often extensive math operations
- Require more and quantitative data
- Provide numerical outcomes that can be compared with known risks
Release Assessment
Determines probability that resistant bacteria will be present in animals as a result of the antimicrobial use.

Exposure Assessment
Gauges the likelihood that humans would ingest the resistant bacteria.

Consequence Assessment
Assesses the chances that human exposure to the resistant bacteria would result in adverse human health consequences.

Overall Risk Estimation (high, medium or low)

FDA DENIAL of product approval and use

FDA APPROVAL UNDER SPECIFIC USE CONDITIONS BASED ON ANTIBIOTIC CLASS, e.g.:
- Prescription only • No extra-label use
- No “prevention” use • No whole herd/flock use
- Limits on duration of use
- Limits on method of administration
- Veterinary Medicine Advisory Committee review

How do companies use Guidance #152?

- Early default assessment of new products/indications
  - Does the concept fit with Guidance #152?
  - What hurdles would be expected?
  - Guides the “pursue or drop” development decisions

- Provides the template for studies, data collection, and dossier outline
  - Companies seek FDA concurrence on research approaches to answer questions
  - Companies provide data and interpretations of research; FDA reviews & questions
Virginiamycin
(Vancomycin resistant - Quinupristin-dalfopristin resistant *E. faecium*)

- The first scenario assumes that 10% of the risk of acquiring resistant streptogramin-resistant *E. faecium* in the hospital is due to a food pathway.
- Average risk to a random hospitalized member of the US population ranges from 6 to 120 chances in 100 million in one year. For a random member of the general US population, the risk estimates range from 0.7 to 14 chances in 100 million in one year.

- Cox et al.
  - Model shows a ban on VM would reduce average treatment failures by 1.8 cases over 5 years and mortalities by 0.29 cases

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Risk Management Components

- **Risk Evaluation**
  - Comparison of the risk assessment outcome to acceptable level of risk

- **Option Evaluation**
  - Process of identifying, evaluating the efficiency and feasibility of, and selection of measures to reduce the risk

- **Implementation**
  - Following through with the risk management decision and ensuring that the risk management measures are in place

- **Monitoring and Review**
  - Auditing process to ensure that results expected are being achieved without unexpected adverse impacts
Risk Assessment Pathway

Food Animals → Meat → Patients

- Release
- Exposure
- Consequence

Risk assessment helps determine appropriate intervention points and the subsequent effectiveness of actions to protect human and animal health

Guides Responsible Use, Regulatory decisions, Food Safety actions

Summary

- Risk assessment process is critical to making science-based decisions on animal antibiotic use
  - Risk estimate helps to prioritize risk-reducing efforts
  - Current feed antibiotic risks are very low!
  - Risk assessment can help to identify appropriate interventions and probable outcomes
  - Data gaps can be identified for further research
    - AMR surveillance, on-farm antibiotic use data, human food borne disease estimates and treatment outcome data
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

Guidelines for use of the precautionary principle

- The precautionary principle should be informed by three specific principles:
  - implementation of the principle should be based on the fullest possible scientific evaluation. As far as possible this evaluation should determine the degree of scientific uncertainty at each stage;
  - any decision to act or not to act pursuant to the precautionary principle must be preceded by a risk evaluation and an evaluation of the potential consequences of inaction;
  - once the results of the scientific evaluation and/or the risk evaluation are available, all the interested parties must be given the opportunity to study of the various options available, while ensuring the greatest possible transparency.

- Besides these specific principles, the general principles of good risk management remain applicable when the precautionary principle is invoked. These are the following five principles:
  - proportionality between the measures taken and the chosen level of protection;
  - non-discrimination in application of the measures;
  - consistency of the measures with similar measures already taken in similar situations or using similar approaches;
  - examination of the benefits and costs of action or lack of action;
  - review of the measures in the light of scientific developments.
  - the burden of proof
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)
Additional (Possible) Approaches to Risk Mitigation (1)

- Veterinary involvement for all antimicrobial uses
- Animal-side diagnostic tests – ID pathogen and resistance gene expression to tailor treatment more effectively
- Pre-harvest and at-harvest pathogen-reduction programs
  - Food safety vaccines
  - HACCP
  - At-harvest antimicrobial intervention
- Improvements in susceptibility surveillance programs that make them truly “prevalence” tools
- Understand “probabilistic” vs “possibilistic” aspects of antibiotic resistance

Additional (Possible) Approaches to Risk Mitigation (2)

- Management changes
  - All in, all out, all clean in between
  - Improve transport-related biosecurity
  - Reduce commingling and subsequent dispersal of animals
- Education
- Incentivize R&D investment
- Longer exclusivity times for those companies that invest significantly in “boots on the ground” technical assistance in judicious use education and monitoring.
Examples of national antibiotic susceptibility monitoring programs

- Canada: Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- Denmark: DANMAP
- Netherlands: Monitoring of Antimicrobial Resistance and Antimicrobial Usage in Animals in the Netherlands (MARAN)
- US: National Antimicrobial Resistance Monitoring System (NARMS)
Conceptual model of most monitoring programs

Resistance in bacteria from live animals on farm
   Assumption: AB use on farm is a key influencer

Resistance in bacteria at animals at slaughter
   Assumption: link to on-farm AB use

Resistance in bacteria on retail meat
   Assumption: bacteria comes from farm

CIPARS 2009: Figure 26. Temporal variation in resistance to selected antimicrobials in Salmonella isolates from pigs; Farm Surveillance, 2006–2009.

CIPARS 2009: Figure 31. Temporal variation in resistance to selected antimicrobials in Escherichia coli isolates from pigs; Farm Surveillance. 2006–2009.
CIPARS 2009: Figure 35. Temporal variation in resistance to selected antimicrobials in *Escherichia coli* isolates from pork; *Retail Meat Surveillance*, 2003–2009.

Difficulties with susceptibility monitoring systems

- Differences in national systems
- Local law limitations/requirements
- Costs to globalize programs
- Statistical validity of trend analysis
- Link between segments
Responsible use by veterinarians

Responsible Use Guidelines

- WVA
- Codex
- OIE
- WHO
- EPRUMA
- AVMA
- Many others…
Judicious use and responsible stewardship

- Unique challenges: Population medicine
  - Barn, farm or geographic location
- What we are doing to meet these challenges
  - Preventive medicine
  - Biosecurity
  - Disease surveillance
  - Best management practices

Appropriate Antibiotic Use in Animals

**LOCALLY**
- Prevention first
  - Patient health/husbandry/sanitation/nutrition/vaccination
- Consult veterinarian for proper animal health intervention
- Proper diagnosis to select appropriate antimicrobial
- Use approved antimicrobials for treatment, minimizing extra-label use
- Treat as long as necessary to effect a cure
- Maintain accurate records of treatment and outcome

**GLOBALLY**
- Better producer education programs
- Better vet services and distribution systems in developing countries for vaccine/medicine use
Prophylactic use of antimicrobials

33. Use of antimicrobials for prevention of disease can only be justified where it can be shown that a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a substitute for good animal health management.

34. Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped. Efforts to prevent disease should continuously be in place aimed at reducing the need for the prophylactic use of antimicrobials.

D. Antimicrobial growth promoters

18. Use of antimicrobial growth promoters that belong to classes of antimicrobial agents used (or submitted for approval) in humans and animals should be terminated or rapidly phased out in the absence of risk-based evaluations. The termination or phasing-out should be accomplished preferably by voluntary programmes of food animal producers, but by legislation if necessary.

19. Risk-based evaluations of all antimicrobial growth promoters should be continued. Characterization of the risk may include consideration of the present and potential future importance of the drug to human medicine, its selection of resistance, the potential exposure to humans from resistant bacteria from food animals, as well as other appropriate scientific factors.
OIE Responsible Use
Therapeutic Uses

12. Supply and administration of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the antimicrobial agents used in animals:

a) prescribed by a veterinarian or other authorised person;
b) supplied only through licensed/authorised distribution systems;
c) administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons.

The relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

Veterinarian Oversight includes…

- Establish veterinarian-client-patient-relationship
- Establish herd/flock health care program to minimize disease prevalence
- Obtain accurate disease diagnosis and/or utilize clinical judgment
- Determine need for treatment and appropriate product
- Administer product per label directions or extra-label use algorithm when necessary
- Maintain adequate records of treatment and clinical outcome to guide subsequent use
Why Veterinary Oversight?

- Veterinarians are viewed as having the necessary experience and accountability to prescribe antibiotics as physicians.
- Disease presentation, diagnostics, client relationship and other considerations require veterinary expertise to integrate into a medication decision.
- Consistent with Responsible Use Principles.

Working together going forward

*Building public trust will require work across stakeholders.*

Diagram showing interactions between public confidence, public, veterinarians, farmers, animal health companies, regulatory agencies, packing plants, and retailers.
Summary of Actions and Recommendations

International and National Level

- **Responsible Use**
  - Appropriate veterinary antibiotic use practices described; education, disease prevention

- **Resistance Monitoring**

- **Antimicrobial Usage Monitoring**

- **Regulatory Controls**
  - Risk assessment-based regulatory decisions on microbial food safety guide decisions on product use:
    - Approval with appropriate label indications and use, prescription

- **Research**
  - New products

Going forward as an industry

- Reinforce by action that medicines are not used indiscriminately

- Producers must have protocols ensuring appropriate use, such as
  - Veterinarian *routinely validating* all uses
  - Independent audits to verify appropriate use

- Non-therapeutic uses
  - No rationale seems to comfort to consumers and many in public health

- Improve our communication skills on safeguards
Key Messages

- Risk analysis is product and indication specific
  - all antibiotics are not created equal
- Monitoring / surveillance of resistance trends are important
  - respond to relevant data, not perceptions
- Responsible use by veterinarians is a primary risk mitigator
  - animals get sick and need medicines, just like people

Closing thoughts...

- Contrary to popular belief, veterinarians don’t have that many options for treating diseases.
- Responsibly developing new antibiotics is important to both human and animal health and the regulatory pathway needs to remain transparent and science based, as it is today.
- Ethical companies are investing in alternatives to antimicrobials to control and prevent infectious diseases in animals, but…
- Antibiotics (and new ones) will always be needed for animal and human health