The Future of Antimicrobials – An Industry Perspective

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Animal Health Institute
NIAA conference
November 15, 2012
Overview

• Development and approval process
  – Time and costs to market
• Regulatory Environment
  – Existing older approvals
  – New products
• Market factors influencing development
• Alternative technologies
• Conclusions
Discovery, Approval and Post Approval

Scientific Discovery → 1/20,000 discoveries are successful

Pre-Clinical Trials → Bacterial tests, chemical screens

Pre-Clinical Trials → Acute, chronic toxicity studies, dose ranging

Clinical Trials → Controlled field trials, residue studies

Regulatory Review → FDA's CVM

Product Approval → FR pub.

Monitoring → Adverse reactions

7-10 Years ~ $100 Million
FDA Approval Process

Safety
- Animal
- Environmental
- Human Food Safety

Efficacy

Quality

Residues, impacts on gut flora

Guidance for Industry #152

Potential for resistance selection to impact human health through food
## IFAH 2011 Global Benchmarking Survey
### Length of time from submission of INAD to approval letter

<table>
<thead>
<tr>
<th>Species category</th>
<th>Product type and years</th>
<th>FAP</th>
<th>CAP</th>
<th>Minor species</th>
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<tbody>
<tr>
<td></td>
<td>Pharmaceuticals</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
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<tr>
<td></td>
<td>Pesticide-based</td>
<td>Range</td>
<td>Range</td>
<td>Range</td>
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<td></td>
<td>GMO products requiring</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
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<td>NEPA RA</td>
<td>Range</td>
<td>Range</td>
<td>Range</td>
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<tr>
<td></td>
<td>Biologics new Master</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
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<td></td>
<td>Seed</td>
<td>Range</td>
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<td></td>
<td>Biologicals new</td>
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<td></td>
<td>combinations</td>
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<td></td>
<td>Biologicals conditional</td>
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<td></td>
<td>license</td>
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</tr>
</tbody>
</table>
### IFAH 2011 Global Benchmarking Survey
Costs of New Product Development by species class and product type – USA 2011

<table>
<thead>
<tr>
<th>Species category</th>
<th>Product category &amp; cost estimates $M: product extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FAP</td>
</tr>
<tr>
<td>Pharmaceutical product with new API</td>
<td>mean 38.8</td>
</tr>
<tr>
<td></td>
<td>range 20.0-100.0</td>
</tr>
<tr>
<td>Medicinal in-feed product</td>
<td>mean 26.7</td>
</tr>
<tr>
<td></td>
<td>range 15.0-40.0</td>
</tr>
<tr>
<td>Biologic product</td>
<td>mean 10.8</td>
</tr>
<tr>
<td></td>
<td>range 2.0-30.0</td>
</tr>
<tr>
<td>Pesticide-based product</td>
<td>mean 14.0</td>
</tr>
<tr>
<td></td>
<td>range 10.0-20.0</td>
</tr>
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</table>
Regulatory History

• Antimicrobial use in food animals has been debated for nearly 40 years.
• Mountains of literature have been produced and many concerns (real or perceived) have been raised on the issue.
• Regulatory policy has been shaped over this time leading to a relatively restrictive regulatory environment (Guidance # 152)
Regulatory History

- 1988 – FDA declares that all new antibiotics must be approved only as prescription drugs.
- 1995 – VFD passed by Congress specifically for animal antimicrobials used in feed.
- 1996 – NARMS implemented to track resistance.
- 1997 – FDA publishes “No ELDU” list.
- 2003 – GFI #152 – Qualitative “Risk Assessment” that all new products must go through.
Regulatory History

• 2008 – GFI # 209 – FDA policy to phase out AGP use and move to VFD for all “medically important antibiotics”

• 2011 – Cephalosporins added to ELDU restrictions.

• 2012 – GFI # 213 – describes process to phase out growth promotion and move to VFD.

• 2012 – Changes to VFD regulation proposed.
Current Antibiotic Uses in Animals

- Disease treatment
  - Therapeutic
- Disease control
  - Therapeutic
- Disease prevention
  - Therapeutic
- Performance or “Growth promotion”

Draft FDA CVM Guidance 209
Antibiotic Uses

Efficacy

Disease Treatment
Administration of an antimicrobial to an animal or group of animals which exhibit clinical disease

Disease Prevention
Administration of an antimicrobial to exposed healthy animals considered to be at risk, but prior to expected onset of disease

Disease Control
Administration of an antimicrobial to animals, usually a flock or herd, in which morbidity and/or mortality has exceeded baseline norms

Growth, or Health maintenance
Administration of an antimicrobial, usually as a feed additive, over a period of time to growing animals that results in improved performance, i.e. weight gain or feed conversion

Therapeutic Uses -- AVMA, FDA, CODEX

Definitions from Clinical and Laboratory Standards Institute
Future Antibiotic Uses in Animals

Efficacy

- Disease treatment
- Disease control
  - Therapeutic
- Disease prevention
  - Therapeutic
- Performance or “Growth promotion”
  - Limited to non-medically important antimicrobials

Draft FDA CVM Guidance 209
Older Approvals
GFI #209/213 and VFD

• FDA will move to phase out AGP uses on “medically important” antibiotics used in feed over next 3-5 years depending on regulatory timelines.
• Medically important = penicillins, tetracyclines, macrolides, lincosamides, streptogramins, potentiated sulfas.
• Marketing status will change from OTC to Veterinary Feed Directive or Rx for approved NADA’s. Over 200 NADA’s affected.
Other Approved Dosage forms

- Medically important Antimicrobials:
  - Injectable
  - Boluses/Tablets
  - Oral drinking water solutions
  - Intramammary infusions

- FDA likely to require these products to carry the Rx legend in the future and will no longer be available as OTC products in farm/feed stores.
New Products
Recent Antimicrobial Development

- All antibiotics approved for short duration/RX/VFD
- New formulations of existing antibiotics
- No products approved for herd/flock administration
- 2 Product approvals withdrawn by FDA (FQ’s in poultry)
- One product rejected by FDA Advisory Committee (Cefquinone)
- 2 Classes restricted for ELDU (FQ’s, Cephs)
# New Antibiotics in last 15 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Class</th>
<th>Species</th>
<th>Dosage Form</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Enrofloxacin</td>
<td>Fluoroquinolone</td>
<td>Beef Cattle, Pigs</td>
<td>Injectable</td>
<td>BRD, SRD</td>
</tr>
<tr>
<td>1998</td>
<td>Florfenicol</td>
<td>Phenicol</td>
<td>Beef Cattle, Pigs, Fish</td>
<td>Injectable, Water, VFD</td>
<td>BRD, SRD, enteric disease</td>
</tr>
<tr>
<td>2002</td>
<td>Danofloxacin</td>
<td>Fluoroquinolone</td>
<td>Beef Cattle</td>
<td>Injectable</td>
<td>BRD</td>
</tr>
<tr>
<td>2005</td>
<td>Tulathromycin</td>
<td>Macrolide</td>
<td>Cattle, Pigs</td>
<td>Injectable</td>
<td>BRD, Foot Rot, IBK, SRD</td>
</tr>
<tr>
<td>2011</td>
<td>Gamithromycin</td>
<td>Macrolide</td>
<td>Beef Cattle</td>
<td>Injectable</td>
<td>BRD</td>
</tr>
<tr>
<td>2012</td>
<td>Tildipirosin</td>
<td>Macrolide</td>
<td>Cattle</td>
<td>Injectable</td>
<td>BRD</td>
</tr>
<tr>
<td>2012</td>
<td>Tylavalosin</td>
<td>Macrolide</td>
<td>Pigs</td>
<td>Water</td>
<td>Ileitis, PPE</td>
</tr>
</tbody>
</table>

1995/96 – Sarafloxacin/Enrofloxacin approved in chickens and turkeys but later withdrawn by FDA.
Impact of GFI #152

• Portrayed as qualitative risk assessment but actually is all about risk management.

• Three components:
  – Release of AR pathogens/commensals (from the animal)
  – Exposure (in food)
  – Consequence (importance to human medicine)

• Adds up to an overall risk of HIGH, MEDIUM, or LOW
Table 8: Examples of potential risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals based on the level of risk (high, medium or low)

<table>
<thead>
<tr>
<th>Approval Conditions</th>
<th>Category 1 (H)</th>
<th>Category 2 (M)</th>
<th>Category 3 (L)</th>
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<tbody>
<tr>
<td>Marketing Status</td>
<td>Rx</td>
<td>Rx, VFD</td>
<td>Rx, VFD, OTC</td>
</tr>
<tr>
<td>Extra-label Use</td>
<td>ELU restrictions</td>
<td>Restricted in some cases</td>
<td>ELU permitted</td>
</tr>
<tr>
<td>Extent of Use</td>
<td>L</td>
<td>L, M</td>
<td>L, M, H</td>
</tr>
<tr>
<td>PAMP (e.g. NARMS)</td>
<td>Yes</td>
<td>Yes</td>
<td>In some cases</td>
</tr>
<tr>
<td>Adv. Com. Rev?</td>
<td>Yes</td>
<td>In certain cases</td>
<td>No</td>
</tr>
</tbody>
</table>
Likely Candidates for Future Development

• Nonhuman use antimicrobial classes or unique analogs within human use classes seem to be preferred to minimize cross-resistance concerns in food-borne bacteria;

• Lack of genetically encoded resistance mechanisms of consequence to human pathogen resistance would seem to be preferred;

• Prescription or Veterinary Feed Directive requirement to encourage veterinarian stewardship; and,

• Administration via injection to individual animals for less than 6 days, or for selected pens or groups of animals to be orally treated under specific use conditions
FDA’s Animal Antibiotic Sales Data, 2010

Source: FDA, CVM 10/31/2011
Ionophores: Not used in Human Medicine

Annual totals (kg)

NIR:
Aminocoumarins
Amphenicols
Diaminopyrimidines
Fluoroquinolones
Glycolipids
Pleuromutilins
Polypeptides
Quinoxalines
Streptogramins

Aminoglycosides
Cephalosporins
Ionophores
Lincosamides
Macrolides
Penicillins
Sulfamethoxazole
Sulfas
Tetracyclines
NIR

Sulfa category includes TMP sulfa.

NIR=Not Independently Reported. Antimicrobial classes for which there were less than 3 distinct sponsors actively marketing products domestically were not independently reported.

Source: FDA, CVM 10/31/2011
Drugs the FDA Deems Critical to Human Health Represent a Very Small Percentage of Sales

Source: FDA, CVM 10/31/2011
Future Development of Antimicrobials

• The future availability of novel antimicrobial agents for use in food animals should also be considered from the often overlooked perspective of world food production needs.

• Global food demand in 2030 is estimated to increase substantially with a commensurate increase in livestock and poultry production.
Antimicrobial Development

• The development of novel anti-infective modalities will need to seek to meet the needs of both human health and food safety with animal health and veterinary medicine.

• The challenge lies in whether these needs are viewed as mutually exclusive objectives by regulatory and public health agencies.
Antimicrobial Development

- FDA is fundamentally changing how existing antimicrobials are used in feed.
- Manufacturers will be very selective about what is researched and developed because of time and cost to satisfying safety requirements.
- Public acceptance will also be a factor in future development plans.
- Worldwide regulatory policies will also have an impact particularly Europe.
Antimicrobial Development

• A host of animal-species specialty organizations have elaborated guidelines on antimicrobial use in food animals.

• Whether it is Prudent Use, Judicious Use, Responsible Use, or Clinical Practice Guidelines, there are certain themes that can be identified which will tend to guide antimicrobial development.
Criteria guiding development

• To avoid cross-resistance, non-human use narrow spectrum antimicrobial classes (or unique analogs) are preferable;

• To minimize co-resistance and cross-resistance selection, a bactericidal mechanism is preferable over a bacteriostatic mechanism;

• Appropriate label directions to guide end-user in use of the product to ensure minimal (to no) selection of food-borne bacteria resistance;
Criteria

• Parenteral route of administration is preferable when possible; oral (water and feed) medications are acceptable for group treatment when injectable products are not feasible (e.g., poultry or swine); and

• Regulatory acceptance of human microbial food safety risk-based evaluations.
Risk Management Strategies

• 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;

• The creation of formularies that serve to direct veterinarians in which products to use or avoid, based in part on human importance ranking lists;

• The need for antimicrobial susceptibility testing methods and clinical breakpoints to enable laboratory testing results to guide the selection of an appropriate product;
Risk Management

• 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); and

• Recommendations ensuring oversight of feed antibiotic use by veterinarians.
**Ideal Antimicrobial**

- What does the ideal antimicrobial product look like?
  - Fundamental quality, safety, and effectiveness components sufficient to meet regulatory requirements.
  - Patent protection.
  - Affordability and acceptable return on investment.
  - Market differentiation from existing products (e.g., improved effectiveness, shorter withdrawal time, etc.).
Ideal Antimicrobial

• Not a member of the Critically Important Antibiotic list—especially those classes used in human medicine to treat food-borne disease, e.g., salmonellosis, campylobacteriosis, or potentially have cross- or co-resistance transfer concerns.

• Bactericidal activity (likely preferable to a bacteriostatic mechanism of action) by a novel mechanism of action, perhaps using a target distinct from existing antimicrobial classes, and have negligible capacity for resistance selection.

• Rapid metabolism into non-microbiologically active constituents, with further degradation in excreta or environment.
Alternative technologies
Past and Future Sources of Animal Health AB Substrate

### Human Health Programs
- MRSA
- MDR Pneumococci
- MDR Gram-Negatives
- MDR TB

### Animal Health Programs
- Livestock
- Respiratory Disease
- Enteric Disease
- Companion Animals
  - SSTI
  - UTIs

**2000s – HH and AH targets have diverged**

This severely limits the ability of AH to leverage substrate!
Where can Animal Health go for new and novel substrate?

- Traditional substrate (small molecules)
  - Novel Classes
    - Discarded by human health programs due to delivery or safety issues that are not as significant of concern in animal health
    - Always at risk due to re-entry of Human health into class
  - Re-exploration of older generations of existing classes
    - Initiate chemistry program to develop novel analogs within an older class that are no longer an important therapeutic class in human health
      - Tune spectrum for veterinary use
      - Resource intensive due to chemistry needs
      - Must clearly understand any resistance selection pressure from use
    - Consideration must be given to “critically important” human health antimicrobials
      - Colistin
Alternative Drug Targets and Substrate

• Distinguished from traditional small molecules
  – Targeting other mechanisms that affect an organism's ability to cause disease, but does not inhibit growth (i.e. virulence)
  – Large molecule substrate (i.e., peptides, antibodies, phage lysins)
  – Bacteriophages (Bacterial viruses)
• Sometimes referred to as “Alternatives to Antibiotics”
  – Not classic small molecule antibiotics
  – Are novel anti-infectives (antibacterials)
Antimicrobial Peptides

- Important component of host innate immune system
  - Not to be confused with peptide antibiotics (e.g., Nisin)
- Bridge the gap between infection onset and adaptive immune response
- Broadly categorized into two major families
  - Defensins
    - Found in both vertebrates and invertebrates
    - Cystine rich cationic proteins containing 6-8 conserved residues, disulphide bonds
    - Produced in neutrophils and epithelial cells
    - 18–45 AA
  - Cathelicidins
    - Contain a highly conserved cathelin region
    - Produced in neutrophils and macrophages
    - 10 – 50 AA enriched in hydrophobic and cationic amino acids

Ramanathan et al., Microbe Inf. 2002
Bacteriophage Therapies

- Act by attaching to specific receptors on bacterial host cell
  - Very specific (“narrow spectrum”), single monophages generally have two or more specific determinants
  - Primarily cell surface receptors, often membrane porins or cell wall components
    - ie. OmbC, OmpB, LPS in Gram(-) and peptidoglycan, teichoic acid in Gram(+)
    - Targeted binding domains are most often critical to bacterial virulence
- Due to specificity disease treatment will likely limited to simple infection types
  - *Pseudomonas aeruginosa* in canine otitis media
- Phage resistance may develop quickly due to changes in the receptor or by changes in host cell strain populations
  - Governed by predator-prey dynamics
  - For this reason a cocktail of multiple monophages are recommended for sufficient coverage
Conclusions

THE FUTURE IS NOW!

• Clear regulatory roadmap for traditional antimicrobials
• More restrictions on current approvals
• Limited development of new antimicrobials particularly “medically important”
• Fewer new applications in feed/water/prevention
• Increasing cost and time for development
• Need for development of new avian antibiotic products
• Developing newer technologies will be important as greater restrictions on conventional antibiotics are enforced
Conclusions

- Animal health needs to develop novel anti-infectives that address the human health cross-resistance concerns while focusing on the health of the animal and the need to provide safe and affordable food to a growing population.

- There is no reason to exclude any substrate that can be effectively exploited for therapeutic uses as long as animal and human safety can be assured.

- The regulatory pathway for development of “alternative” agents will be the same as for traditional agents.
  - Efficacy and Safety will remain key to the approval process
  - Other areas (safety, manufacturing, etc) may be the most challenging aspect
  - Timelines will be the same as for traditional agents if not longer
    - 8-12 years
  - The fact remains that there are currently no viable alternatives to therapeutic antibiotics for disease treatment