Role of Antimicrobial Resistance in the Approval of Antimicrobial Drugs for Human Food Animals

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Evaluation of Human Food Safety

Components of Human Food Safety package

Toxicology - Evaluation of toxicological effect of drug residues on human health

Microbial food safety - Evaluation of the hazard of developing resistant bacteria
- Effect on human gut flora

Residue chemistry - Evaluation of drug residues in the edible tissues of food animals
CVM’s Human Food Safety Assessments

- Toxicology - Dr. Haydée Fernández
  - How the assessment on effects on intestinal flora influences the ADI for a drug

- Microbial Food Safety - Dr. Silvia A. Piñeiro
  - Role of antimicrobial resistance in the approval of antimicrobial drugs for food animal

- Residue Chemistry - Dr. Lynn G. Friedlander
  - Role of Residue Chemistry in the approval of animal drugs
CVM’s Human Food Safety Assessments

Microbial Food Safety assessment –

- As a public health issue, determines the likelihood of emergence and dissemination of antimicrobial resistant pathogens in or on food-producing animals, that may affect humans by exposure through food-borne pathway.

- Addressing antimicrobial resistance issues.
Role of Antimicrobial Resistance in the Approval of Antimicrobial Drugs for Human Food Animals

- Antimicrobial Resistance and its importance

- The Agency's role in managing Antimicrobial Resistance through careful evaluation of antimicrobial new animal drugs used in food-producing animals
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General Concepts

- Antimicrobial resistance is an inevitable biological consequence of antibiotic use. Given sufficient time and use, resistance will appear (at least so far…) and spread.
- Use of antimicrobials by one individual affects others in the extended and immediate environment.
- Historically, resistance has been progressive, evolving from low levels, through intermediate to high levels.
  - Currently, MDR appears from a single genetic event
- Bacteria that are resistant to one antimicrobial are likely to become resistant to others.
- Once resistance appears, it is likely to decline slowly, if at all.
- Antimicrobial use promotes the development and spread of new mutations and gene arrangements.
- The challenge is to control and contain development of resistance to protect human health.
The Nobel Prize in Physiology or Medicine 1945
"for the discovery of penicillin and its curative effect in various infectious diseases"

Sir Alexander Fleming
Presentacion en la entrega del Premio Nobel, December 11, 1945

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”
The “Golden Age” of Antibiotics
Timeline: Antibiotic Drug Discovery

1908
- Protonsil (sulfonamide)

1932
- Salvarsan (arsenical)

1940
- (1940-1950)
  - Gramicidin (peptide)
  - Penicillin (β-lactam)
  - Neomycin (aminoglycoside)
  - Streptomycin (aminoglycoside)
  - Cephalosporin (β-lactam)

1950
- (1950-1960)
  - Chloramphenicol (phenylpropanoid)
  - Chlortetracycline (tetracycline)
  - Polymyxin (lipopeptide)
  - Erythromycin (macrolide)
  - Vancomycin (glycopeptide)
  - Virginiamycin (streptogramin)

1960
- Rifamycin (ansamycin)

1962
- Nalidixic acid (quinolone)

2000
- Linezolid (oxazolidinone)

2003
- Tigecycline (glycylcycline)

2005
- Daptomycin (lipopeptide)

Antibiotic class is shown in brackets.
Most Challenging Pathogens

**MRSA** – Recently became a community infections. Pediatric infections rose 28% in three years.

**VRE** – A major cause of HAI. One effective agent available for treatment. Feared transfer of resistance to Staph has occurred in 3 states.

**Acinetobacter baumanii** - Battlefield infections that has spread inside hospitals. Increasingly common cause of pneumonia, now 7% of hospital-acquired cases. Few/no treatment options. >40 R-genes

**Aspergillus** – Immunocompromised are at risk of being infected with this fungus. Bloodstream aspergillus kills 50% of the time or more despite treatment.

**E. coli & Klebsiella** - Major causes of urinary tract, gastrointestinal and wound infections. Some Klebsiella pneumoniae virtually untreatable.

**Pseudomonas aeruginosa** – Widespread MDR. Particular risk in patients with CF.
Other Important MDR Pathogens

- *Mycobacterium tuberculosis*
- *Enterobacter cloacae*
- *Streptococcus pneumoniae*
- *Hemophilus influenzae*
- *Salmonella enterica*
- *Neisseria gonorrhoeae*
- *Shigella dysenteriae*
- *Bacteriodes spp.*
- *Stenotrophomonas maltophilia*
- *Burkholderia cepacia*

*Other viruses, parasites and fungi*
Impact of Resistance

1. More expensive drugs

2. Additional diagnostic testing

3. Extended length of stay in the hospital

4. Costs to patient/family-time from work, early death

5. Resistance genes remain a problem for the future – the hospital as reservoir
Clinical & Laboratory Standards Institute (CLSI) Definition:

“Resistant strains are not inhibited by the usually achievable systemic concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy has not been reliable in treatment studies”.

Growth inhibition by antibiotics is quantified by measuring the minimum inhibitory concentration or MIC.
Definitions of Antimicrobial Resistance

- *Intrinsic*: natural to all members of a *sp.*
- *Acquired*: present in certain isolates
  - *Mutations*: alteration of the target (low transmissibility)
  - *Added gene*: antibiotic resistance genes from other bacteria in several ways (high transmissibility)
How does resistance develop?

How does resistance spread?
Antibiotic Resistance Mechanisms

1. Drug
2. Drug Target
3. Permeability

1. Enzymatic inactivation or modification
   β-lac., AGL, CML

2. Target site mutation (may also extend spectrum or level of R)
   β-lac, STR, MAC, FQ

2. Target substitution
   sulfa drugs

2. Target modification
   TET, MAC

3. ↓ uptake or ↑ efflux
   β-lac TET, MAC, FQ

From SB Levy, Scientific American, 1998
## Examples of mechanisms of antibiotic resistance in bacteria

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Method of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>reduced uptake into cell</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>active efflux from the cell</td>
</tr>
<tr>
<td>β-lactams, Erythromycin, Lincomycin</td>
<td>eliminates or reduces binding of antibiotic to cell target</td>
</tr>
<tr>
<td>β-lactams, Aminoglycosides, Chloramphenicol</td>
<td>enzymatic cleavage or modification to inactivate antibiotic molecule</td>
</tr>
<tr>
<td>Sulfonamides, Trimethoprim</td>
<td>metabolic bypass of inhibited reaction</td>
</tr>
<tr>
<td>Sulfonamides, Trimethoprim</td>
<td>overproduction of antibiotic target (titration)</td>
</tr>
</tbody>
</table>
How does resistance develop?

How does resistance spread?
“What is responsible for the widespread dissemination and diversity of drug resistance determinants?”

Mutation/Propagation

Genetic Mutation Causes Drug Resistance

- Non-resistant bacteria exist
- Bacteria multiply by the billions
- Some mutations make the bacterium drug resistant
- Drug resistant bacteria multiply and thrive.

Mutation in DNA

Credit: NIAID
“What is responsible for the widespread dissemination and diversity of drug resistance determinants?”

Accumulation/Dissemination (plasmids, integrons, transposons, etc)

Credit: NIAID
Mechanisms of horizontal gene transfer in bacteria
Gene Exchange in Bacteria

Conjugation
Plasmids, Conj. Tn

Transformation

Transduction
Mobile Resistance Genes

- **Plasmids**
  - Self replicating, non-essential DNA that mediates its own transfer (conjugative)
  - Can carry multiple accessory genes
  - May reversibly incorporate into the chromosome

- **Transposons**
  - “Jumping genes”
  - Can possess multiple resistance genes, as well as integrons
  - Can move freely between chromosome and plasmids
  - May be conjugative

- **Integrons**
  - “Gene catchers”
  - co-selection of tandem gene arrays
  - On plasmids and chromosomes

- **IS Common Regions**
  - Mega MDR elements, etc…..
Microbial Gene Exchange

Resistance spreads by gene exchange and clonal expansion
Environmental Spread

Drinking water

Manure spreading

Farm effluents

Offal

Commercial food animal processing

Handling preparation consumption

Meat

Contact

Animal feeds

Water

Sewage

Travel
Uses of Antimicrobials in Food Animal Production

- **Therapy** - to *treat* diseased animals
- **Metaphylaxis** - to *control* outbreaks of disease
- **Prophylaxis** - to *prevent* infections
- **Non therapeutic uses** - to *increase feed efficiency* (improve feed efficiency, increase rate of weight gain)
  - Complicated by overlapping claims
  - Most controversial, since drugs are administered continuously to healthy animals
  - Many consider this use to pose an unnecessary risk
Using Antimicrobials in Food-Producing Animals may Result in:

- Increase in the number of human pathogenic bacteria in the intestinal flora of the animal (e.g., *Salmonella*)
- Selection of resistant bacteria in the intestinal flora of the animal
- Transfer of resistant bacteria to humans (consumption of contaminated food)
- Transfer of resistant genes to human bacteria
- Increase in the incidence of human infections caused by pathogenic resistant bacteria
- Potential therapeutic failure in humans
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Microbial Food Safety For Antimicrobial Drugs

Guidance for Industry (GFI) #152

“Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern.”

http://www.fda.gov/cvm/Documents/fguide152.pdf
Guidance for Industry (GFI) #152

- Addresses the association of antimicrobial resistance with use of antimicrobial drugs in food animals
- Selection of resistant bacteria in treated animals that may translate to resistant bacteria in humans
Guidance for Industry # 152

Objective:

To provide safe use of antimicrobials in food-producing animals while ensuring that important human therapies are not compromised or lost.
Guidance for Industry # 152

- Qualitative risk assessment approach to evaluate the microbial food safety of new antimicrobial drugs for use in food animals (risk of creating resistance).

- The approach applies to all uses of all antimicrobial drugs intended for food-producing animals.
The scope of this document is an assessment of the effect of the transmission of foodborne bacteria of human health concern through the consumption of animal derived food products.

Although FDA’s primary focus will be foodborne pathogens, other bacterial hazards may be considered when deemed necessary.

1st step: Hazard Characterization

2nd step: Qualitative Risk Assessment
Defining/Characterizing a Hazard and Risk Assessment

The hazard has been defined as human illness, (that is)
- caused by an antimicrobial-resistant bacterium,
- attributable to an animal-derived food commodity, and
- treated with a human antimicrobial drug of concern.

The risk is defined as the probability that human food-borne illness
- is caused by an antimicrobial-resistant bacteria,
- is attributable to an animal-derived food commodity, and
- is treated with the human antimicrobial drug of interest.

Hazard Characterization: Part of the risk evaluation

Qualitative Risk Assessment: release, exposure, and consequence assessments
Hazard Characterization

Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment

Risk Estimation
Hazard Characterization

FDA recommends that sponsors address the hazard characterization step of the risk assessment by submitting information regarding:

- chemical,
- biochemical,
- microbiological, and
- physical properties

of the antimicrobial new animal drug that bear on characterizing the downstream effects of the drug (GFI # 152, p. 8)
Hazard Characterization, cont’d

A hazard characterization *may* satisfy microbial food safety concerns in some cases, such as:

- Drugs not listed in the Appendix A, GFI #152;

- Compounds that have unique use patterns/formulations/activity and other specific information to mitigate concerns;
Hazard Characterization, cont’d

Possible components:

- Drug-specific information
- Bacterial resistance information
- Data gaps and emerging science
Hazard Characterization

Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment

Risk Estimation
Hazard Characterization

Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment

Risk Estimation
Qualitative Risk Assessment

- Main elements:
  - Development of resistance among bacteria in/on treated food-producing animals
  - Human exposure
  - Human health consequences

- Risk assessment is essential for risk estimation and risk management
Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment

Risk Estimation
Qualitative Risk Assessment

- Describes factors related to an antimicrobial drug and its use in animals that contribute to the emergence of resistant bacteria or resistant determinants in the animal.
- Estimates the probability of emergence or selection of resistant bacteria in food–producing animals as a result of the use of an antimicrobial drug.
Factors for the Release Assessment, cont’d

<table>
<thead>
<tr>
<th>Release parameters (examples)</th>
<th>Release assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of activity</td>
<td>High, Medium, Low</td>
</tr>
<tr>
<td>Spectrum of activity</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td></td>
</tr>
<tr>
<td>Resistance mechanisms</td>
<td></td>
</tr>
<tr>
<td>Resistance transfer</td>
<td></td>
</tr>
<tr>
<td>Selection pressure</td>
<td></td>
</tr>
<tr>
<td>Others (data gaps)</td>
<td></td>
</tr>
</tbody>
</table>
Hazard Characterization

Qualitative Risk Assessment

Release Assessment
Exposure Assessment
Consequence Assessment
Risk Estimation
Qualitative Risk Assessment

Release Assessment

Exposure Assessment

Consequence Assessment

Risk Estimation

Hazard Characterization
Exposure Assessment

Describes likelihood of human exposure to food-borne bacteria of human health concern through animal-derived food products.
Exposure Assessment

<table>
<thead>
<tr>
<th>Probability of food commodity contamination</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment

Risk Estimation
Qualitative Risk Assessment

Release Assessment

Exposure Assessment

Consequence Assessment

Risk Estimation
Qualitative Risk Assessment

Consequence Assessment

Describes human health consequences of exposure to resistant bacteria based on importance of drug (or related drugs) to humans (ranking of antimicrobials)

Estimates probability that human exposure to resistant bacteria results in an adverse health consequence.
Ranking of Antimicrobial Drugs

- Importance of antimicrobial drugs used in human medicine
- Provided by FDA’s Center for Drug Evaluation and Research (CDER)
- Based upon five criteria
CDER’s Criteria for Ranking

1. Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease

2. Sole therapy or one of few alternatives to treat serious disease or drug is essential component among many antimicrobials in the treatment of human disease

3. Antimicrobials used to treat enteric pathogens in non-food-borne disease

4. No cross-resistance within drug class and absence of linked resistance with other drug classes

5. Difficulty in transmitting resistance elements within or across genera and species of organisms

**Critically important**: Meet BOTH criteria 1 and 2  
**Highly important**: Meet either 1 or 2  
**Important**: Meet either criteria 3, 4, or 5
Drug Rankings and Examples

- **Critically Important**
  - macrolides, fluoroquinolones

- **Highly Important**
  - aminoglycosides, clindamycin

- **Important**
  - monobactams, quinolones
Risk estimation integrates results from release, exposure and consequence assessments to produce overall measure of risk associated with hazards.
Risk Estimation: Integration of Outcomes

RELEASE:
High, Medium, or Low

coupled with

EXPOSURE:
High, Medium, or Low

coupled with

CONSEQUENCE:
Important, Highly Important, or Critically Important

= RISK ESTIMATION:
High, Medium, or Low
# Examples of Risk Estimation

<table>
<thead>
<tr>
<th>Release</th>
<th>Exposure</th>
<th>Consequence</th>
<th>Risk Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Important</td>
<td>Low</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>Highly Important</td>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Critically Important</td>
<td>High</td>
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<td>Low</td>
<td>Low</td>
<td>Critically Important</td>
<td>High</td>
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<td>Medium</td>
<td>Low</td>
<td>Critically Important</td>
<td>High</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Critically Important</td>
<td>High</td>
</tr>
</tbody>
</table>
The risk rankings of **low**, **medium**, or **high** represent the potential for human health to be adversely impacted by the selection or emergence of antimicrobial resistance in food-borne bacteria associated with the use of an antimicrobial drug in food-producing animals.
Possible *risk management* steps range from denying the approval of a drug application to approving the application under various use conditions that assure the safe use of the product.

Steps may be applied to manage the estimated level of risk.

Overall drug risk estimation (H, M, or L risk) may be coupled with management strategies.
**Extent-of-use Limitations**

Possible process for ranking (High, Medium, Low) of extent of antimicrobial drug use in animals based on duration and method of administration (GFI #152, Table 7, Page 23)

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Intended administration to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual animals</td>
</tr>
<tr>
<td><strong>Short (&lt;6 days)</strong></td>
<td>L$^1$</td>
</tr>
<tr>
<td><strong>Medium (6-21 days)</strong></td>
<td>L</td>
</tr>
<tr>
<td><strong>Long (&gt;21 days)</strong></td>
<td>M</td>
</tr>
</tbody>
</table>
### Examples of Possible Risk Management Strategies Based on the Level of Risk (H, M, or L)

<table>
<thead>
<tr>
<th>Approval conditions</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category 1 (H)</td>
</tr>
<tr>
<td>Marketing status</td>
<td>Rx</td>
</tr>
<tr>
<td>Extra-label use</td>
<td>ELU restriction</td>
</tr>
<tr>
<td>Extent of use</td>
<td>Low</td>
</tr>
<tr>
<td>Post-approval monitoring</td>
<td>NARMS</td>
</tr>
<tr>
<td>Advisory committee review</td>
<td>YES</td>
</tr>
</tbody>
</table>

Prescription (Rx), Veterinary Feed Directive (VFD), over-the-counter (OTC)
Summary of the Microbial Food Safety Assessment Process

FDA recommends that sponsors choosing to use this process:

- Prepare a **hazard characterization** and submit it for review.

- After review of the hazard characterization, discuss with FDA whether a **risk assessment needs to be completed** and, if so, what information is recommended for completion of the risk assessment.

- Prepare the **risk assessment** and submit the assessment to the FDA for review.

- Following review of the safety package as a whole, including the risk assessment, FDA will determine the **risk estimation** and **associated risk management steps** applicable to the proposed conditions of use for the antimicrobial new animal drug.
THANK YOU!