Uses of Antimicrobials in Food Animals

- to treat diseased animals
- to control outbreaks of disease
- to prevent disease
- Non therapeutic uses - to improve feed efficiency and increase rate of weight gain
  - Complicated by overlapping claims
  - Many consider such uses of antimicrobial drugs in food-producing animals for production or growth-enhancing purposes a contributing factor to antimicrobial resistance

Possible public health impact as a result of the use of antimicrobials in food-producing animals

- Increase in numbers of resistant organisms in or on animals as a result of drug use (e.g. Salmonella)
- Transfer of resistance genes to human bacteria
- Selection of resistant bacteria in the intestinal flora of the animal
- Resistant pathogens may contaminate carcasses at slaughter and be transmitted to humans through consumption and handling of contaminated food
- When resistant bacteria cause a human illness that needs treatment, medical therapy may be compromised
To assess the public health impact as a result of antimicrobial use in food producing animals, FDA considers the following:

- As a public health issue, we determine 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. Guidance For Industry (GFI) #152

- As part of an Acceptable Daily Intake (ADI) assessment, we determine the impact of antimicrobial drug residues in edible tissues on human intestinal flora. Guidance For Industry (GFI) #159 (VICH Guideline #36)

Differences between two approaches

- GFI #152 addresses effects of antimicrobial drugs on selection of antimicrobial-resistant bacteria in/on treated food-producing animals

- GFI #159 addresses effects of antimicrobial drug residues in edible tissues on intestinal flora of human consumers

Microbial Food Safety

2003 - Guidance for Industry #152 (GFI #152):

Evaluating the safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Focus of GFI #152:

- Provides an outline for a qualitative risk assessment that focuses on the public health impact as a result of the proposed drug use in food-producing animals to select for antimicrobial-resistant bacteria.

- Assesses risks to human health through the consumption of animal-derived food products (1st pathway exposure to food-borne bacteria). This risk assessment evaluates potential effects of antimicrobial drugs on non-target (food-borne) bacteria (e.g., E.coli, Salmonella, Campylobacter, and Enterococcus spp.), however, other bacterial hazards may be considered.

What is involved in the GFI #152 process?

The GFI 152 process: some considerations in the Risk Assessment

- How will the drug be delivered
- Numbers of animals that will receive treatment
- How specific is claim for the antimicrobial: animal class, life span, how close to processing will drug be delivered?
- Organisms of human health concern and prevalence in target animal
- Drug:bug interaction- current resistance profile and prevalence;
- Selection pressure and resistance dissemination
- Dose and duration of use
The GFI #152 process- Example of a drug product evaluation for Microbial Food Safety:

Drug X is an injectable; critically important drug (see appendix A); For use in cattle for the treatment of bovine respiratory disease

The risk assessment will focus on the proposed use of Drug X specifically in beef cattle and non-lactating dairy cattle

Examples of some considerations in the Risk Assessment for Drug X:

- How the drug will be used in cattle:
  - treat on arrival; details on disease particulars:
    - early/middle/late outbreak
  - specific population of animals: lactating, beef cattle: animal class, life span

- Target animal population and organisms of human health concern:
  - Salmonella, commensal E.coli, Campylobacter

- What are the concerns regarding antimicrobial resistance in these organisms?
  - their current resistance profiles to drug X, including information on MDR linkages
  - prevalence in the target animal environment
  - human health consequences with respect to current treatment;
  - PKPD of Drug X, especially those PK data from the intestine of target animal species

Hazard

Hazard is defined as a human illness.....

- caused by an antimicrobial-resistant bacteria
- attributable to an animal-derived food commodity,
- treated with the human antimicrobial drug of interest

Potential increase in drug X-resistant bacteria in our food supply (Campylobacter, E.coli, Salmonella) associated with the use of Drug X in beef and non-lactating cattle

Specifically:
The hazard is defined as human illness caused by drug X-resistant Salmonella spp., attributable to consumption of contaminated ground beef, and treated with a human antibiotic from the drug X class of antibiotics.
What is involved in the GFI #152 process?

Hazard Characterization

Qualitative Risk Assessment

Release Assessment

Exposure Assessment

Consequence Assessment

Risk Estimation

Release Assessment (RA)

Boundaries of the RA span from the point the new animal drug is administered to the animal to the point the animal is harvested for slaughter (when food is collected for consumption)

Describes factors related to an antimicrobial drug and its use in animals that contribute to the emergence of resistant bacteria or resistance determinants in the animals.

Examples of Drug X Information (within the RA):

• About the product
  Conditions of use (route of administration, dosage regimen, intended animal species, etc.)

• Mechanism and type of antimicrobial action
  Specific antimicrobial resistance (e.g. protein synthesis inhibitor) action (e.g. bacteriostatic vs bactericidal)

• Spectrum of activity
  Active against Gram +/-, and specific susceptibility data
  The information can link index food-borne pathogens and commensals

• The pharmacokinetics/pharmacodynamics of the drug
  e.g. active drug X concentration in the colonic contents
Drug X RA- cont’d

- Resistance mechanisms and genetics
  Known mechanism(s) of resistance, including location of resistance determinants
- Occurrence and rate of transfer of resistance determinants
  How easily is resistance disseminated (by transformation, transduction, conjugation, or transposition)
- Resistance selection pressures
  Extent of use of the proposed product (e.g., duration of administration; individual vs. small groups vs. flocks/herds)
- Baseline prevalence of resistance
  Support with any epidemiological data (e.g. NARMS), current literature, or other sources on prevalence of resistance to the drug

Drug X RA outcome-

- Overall conclusion of the RA estimates the probability that resistant organisms will emerge or be selected for as a consequence of the proposed use of Drug X

- Based on the information provided in the release assessment, and taking into account information that included drug specific characteristics and whether or not each factor would have a high, medium or low likelihood of favoring resistance emergence*, the outcome of the release assessment in this example is determined to be “Medium”

* GFI 152: Table 1: Sample table for collating and summarizing interpretation of relevant factors considered in completing the release assessment

What is involved in the GFI #152 process?

Hazard Characterization

Qualitative Risk Assessment

- Release Assessment
- Exposure Assessment
- Consequence Assessment
- Risk Estimation
Exposure Assessment (EA)

- Evaluation based on relative consumption and contamination rates of the food (target animal) commodity
- Describes likelihood of human exposure to food-borne bacteria of human health concern through the consumption of animal-derived food products
- Food commodity output from cattle production is beef, primary exposure is ground beef.
- Probability that humans consuming beef will be exposed to Drug X resistant bacteria of public health concern
- Variety of data sources- all welcome to better address the concern (NARMS, literature, etc.).

Exposure Assessment cont’d

EXAMPLE - USDA per capita consumption data for red meats, poultry, fish, and shellfish

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Consumption (pounds per capita per year)</th>
<th>Qualitative Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>62.9</td>
<td>HIGH</td>
</tr>
<tr>
<td>Chicken</td>
<td>61.3</td>
<td>HIGH</td>
</tr>
<tr>
<td>Pork</td>
<td>46</td>
<td>HIGH</td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>16.5</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Turkey</td>
<td>13.3</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Lamb</td>
<td>1.1</td>
<td>LOW</td>
</tr>
<tr>
<td>Veal</td>
<td>0.4</td>
<td>LOW</td>
</tr>
<tr>
<td>Total Meat</td>
<td>109.8</td>
<td></td>
</tr>
</tbody>
</table>

GFI #152, Table 2, pg 17. Source: USDA

Exposure Assessment cont’d

USDA data on prevalence of Salmonella contamination of various animal-derived food commodities and qualitative contamination rankings

<table>
<thead>
<tr>
<th>COMMODITY</th>
<th>% BASELINE PREVALENCE</th>
<th>% PREVALENCE 2001/2003</th>
<th>QUALITATIVE RANKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground turkey</td>
<td>49.9</td>
<td>26.2/23.4</td>
<td>HIGH</td>
</tr>
<tr>
<td>Ground Chicken</td>
<td>44.6</td>
<td>19.5/35.5</td>
<td>HIGH</td>
</tr>
<tr>
<td>Broilers</td>
<td>20.0</td>
<td>11.9/12.8</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Market Hogs</td>
<td>8.7</td>
<td>3.8/2.5</td>
<td>LOW</td>
</tr>
<tr>
<td>Ground Beef</td>
<td>7.5</td>
<td>2.8/1.7</td>
<td>LOW</td>
</tr>
<tr>
<td>Cows/Bulls</td>
<td>2.7</td>
<td>2.4/1.5</td>
<td>LOW</td>
</tr>
<tr>
<td>Steers/Heliers</td>
<td>1.0</td>
<td>0.6/0.4</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Drug X- EA outcome:

<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>

* Using Salmonella as an example

What is involved in the GFI #152 process?

Consequence Assessment

- Importance of antimicrobial drugs used in human medicine- ranked as critically important, highly important or important
- 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- GFI 152 Appendix A

- Critically Important
  macrolides, fluoroquinolones
- Highly Important
  aminoglycosides, clindamycin
- Important
  monobactams, quinolones
- Drug X belongs to the ‘critically important’ class of antimicrobials

Overall Risk Estimation

Result is low, medium, or high risk for human health to be adversely impacted by emergence of antimicrobial resistance associated with the proposed use of the drug in animals

Integration of the results from the release assessment, exposure assessment, and consequence assessment for Drug X results in an overall risk estimation of HIGH

<table>
<thead>
<tr>
<th>Release</th>
<th>Exposure</th>
<th>Consequence</th>
<th>Risk Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>HIGH</td>
</tr>
</tbody>
</table>
Based on the overall outcome of the risk assessment, there are various risk management steps available to mitigate risks, ranging from denying the approval of a drug application to approving the application.

Risk Management categories:
Category 1 (high risk estimate) -- strictly limited use conditions
Category 2 (medium risk estimate) -- intermediate restriction on drug use
Category 3 (low risk estimate) -- least restriction on drug use

Risk management considerations for Drug X

<table>
<thead>
<tr>
<th>Approval conditions</th>
<th>Category 1 (High)</th>
<th>Category 2 (Medium)</th>
<th>Category 3 (Low)</th>
</tr>
</thead>
<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>Restricted</td>
<td>Restricted in some cases</td>
<td>Permitted</td>
</tr>
<tr>
<td>Extent of use</td>
<td>Low-injectable-individual animals</td>
<td>Low, medium</td>
<td>Low, medium, high</td>
</tr>
<tr>
<td>Post-approval monitoring</td>
<td>NARMS monitors drug X</td>
<td>NARMS</td>
<td>In certain cases</td>
</tr>
<tr>
<td>Advisory committee review considered</td>
<td>Depends-first approval in class, etc</td>
<td>In certain cases</td>
<td>No</td>
</tr>
</tbody>
</table>

RM considerations for antimicrobials

Extent-of-use limitations –
The Agency thinks extent-of-use limitations is an important factor in determining safe conditions of use of a new animal drug.

<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>Short (&lt;6 days)</td>
<td>L¹</td>
</tr>
<tr>
<td>Medium (6-21 days)</td>
<td>L</td>
</tr>
<tr>
<td>Long (&gt;21 days)</td>
<td>M</td>
</tr>
</tbody>
</table>
In summary GFI #152:

- Considers an antimicrobial new drug to be 'safe' if it concludes that there is a reasonable certainty of no harm to public health from the proposed use of a drug in food-producing animals.

- Is concerned about the decrease (or loss) in effectiveness of antimicrobial drugs in humans as a consequence of human exposure to resistant bacteria through the ingestion of animal derived products.

- Provides a Risk Assessment process to estimate the probability of the occurrence of the hazard.

In summary, the Agency 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 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.

Microbial Food Safety

2006, Guidance for Industry #159

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI – VICH-36

http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123817.htm
**Definition**

What is the microbiological ADI?

An ADI established on the basis of microbiological data. The microbiological ADI is derived from *in vitro* or *in vivo* studies and based on effects of antimicrobial residues on the human intestinal flora. These residues are present in human food from animals treated with the drug.

**When determine a microbiological ADI?**

- Derivation of a microbiological ADI for an antimicrobial is only recommended if, according to VICH GL 36, residues of the drug reach the colon and remain microbiologically active against the human intestinal flora.
- The microbiological ADI may be determined for one or both effects of human health concern:
  - Disruption of the colonization barrier and
  - Increase in the population of resistant bacteria in the human colon.
- Sponsors may present information to request dismissal for addressing one or both adverse effects.

**Disruption of the Colonization Barrier**

- The *colonization barrier* is a normal function of intestinal flora that limits colonization of the colon by exogenous microorganisms as well as overgrowth of indigenous, potentially pathogenic microorganisms.
- Effect on bacteria that protects the normal ecology of the flora.
- Colonization of the intestine by potentially pathogenic bacteria (e.g., *Salmonella*, *E. coli*, *C. difficile*).
Increase in the Population of Resistant Bacteria in the Colon

Increase in the population(s) of normally present bacteria that are insensitive to a drug due to:

- Acquisition of resistance by bacteria that were previously sensitive
- Relative increase in the proportion of less-sensitive bacteria

Addressing the effect of antimicrobial drug residues on human intestinal flora

- Step-by-step approach to determine if drug residues reach the human colon and remain microbiologically active;
- Outlines steps to determine the need for establishing a microbiological ADI;
- Test systems and methods to determine the no-observed adverse effect concentrations/levels (NOAEC/Ls) for endpoints of human health concern;
- Procedures to determine a microbiological ADI from the NOAEC/Ls.
- Data or information required can come from experimentation or scientific literature.

---

Step 1. Are residues of the drug (and/or its metabolites) microbiologically active against representative human intestinal flora? If no information is available, it is recommended that you assume that the compound and (or) its metabolites are microbiologically active.

Step 2. Do residues enter the human colon? Recommended that you assume that 100% of the ingested residue enters the colon remains microbiologically active.

Step 3. Do residues entering the human colon remain microbiologically active? Data demonstrating loss of microbiological activity from in vitro inactivation studies of the drug incubated with feces, or data from in vivo studies evaluating the drug’s microbiological activity in the feces or colon content of animals.

Step 4. Assess whether there is any scientific justification to eliminate the need for testing either one or both endpoints of concern. Disruption of the colonization barrier and increase in the population(s) of resistant bacteria in the human colon.

Step 5. To determine the NOAEC/NOAEL for the endpoint(s) of concern as established in step 4. The most appropriate NOAEC/NOAEL is used to determine the microbiological ADI.

If no information is available, it is recommended that you assume that 100% of the ingested residue entering the colon remains microbiologically active.
Different approaches to calculate a microbiological ADI

- From *in vitro* studies
  - MIC data from representative bacterial groups
  - Test systems that model the human intestinal flora

- From *in vivo* studies
  - Conventional laboratory animals
  - Human flora-associated rodents

Microbiological ADI calculated from *in vitro* studies

- From MIC data of representative bacterial groups of the human colon
  - Usually a conservative ADI
  - A calculated MIC based on MIC50 values of bacterial groups is part of a formula that also includes
    - amount of colon content (220 g)
    - percentage of oral dose available to bacteria
    - weight of a person (60 kg)
  - Test systems that model the human intestinal flora (e.g., fecal slurries, semi-continuous and continuous fed-batch cultures, etc.)
    - May result in a more appropriate NOAEC and possibly a higher ADI
    - Allow testing short-term and long-term exposure of feces to different drug concentrations
    - Several parameters can be measured at once (e.g., changes in bacterial populations, changes in volatile fatty acids, etc.)
    - Many issues are still unresolved with these systems (e.g., dilution rate, duration of drug exposure, reproducibility of the test, etc.)

Microbiological ADI calculated from *in vivo* studies

- Test systems using conventional laboratory animals
  - Differences in the flora with respect to humans
  - They can be tested in higher numbers which allows a more robust statistic analysis of results

- Test systems using human flora-associated (HFA) rodents
  - More similar to human flora once established in the animal
  - Has been used for this purpose internationally
  - Several parameters of the flora can be studied
  - Expensive and requires equipment and special expertise
Examples of Microbiological ADI Determination

For Disruption of Colonization Barrier:

\[ \text{ADI} = \text{MIC}_{50} \times \text{Mass of Colon Content} \times \text{Fraction of one dose} \times 60 \text{ kg person available to microorganisms} \]

MIC<sub>50</sub>: The MIC<sub>50</sub> is derived from the lower (50%) confidence limit for the mean MICs of the relevant genera for which the drug is active, as described in Appendix C.

The final ADI used to calculate the safe concentration and tolerance for antimicrobial drug residues in edible tissues will be either the microbiological or the toxicological ADI, whichever is the lowest.

Final ADI (Toxicological vs. Microbiological)

- Microbiological ADI only applies to antimicrobial new animal drugs or compounds with antimicrobial activity;
- If two microbiological ADIs are determined (one for each endpoint), the lowest one will be the final microbiological ADI;
- The final ADI used to calculate the safe concentration and tolerance for antimicrobial drug residues in edible tissues will be either the microbiological or the toxicological ADI, which ever is the lowest.

In summary...

All antimicrobial drugs or compounds with antimicrobial activity need to address this important Human Food Safety endpoint;

However, a microbiological ADI is not always necessary for all antimicrobial drugs or compounds with antimicrobial activity because
- Microbiologically active residues might not reach and/or remain active in the colon
- The concentration of active residues in the colon is so low that they would probably not affect the integrity of the flora
Microbial Food Safety is one component of the Human Food Safety evaluation

Toxicology
Evaluation of toxicological effect of drug residues on human health

Microbial food safety
- Evaluating the effects of the hazard on the development of antimicrobial-resistant bacteria
- Effect on human gut flora

Residue chemistry
Evaluation of drug residues in the edible tissues of food animals

THANK YOU!

Microbial Food Safety Team (HFV-157)
Division of Human Food Safety
Office of New Animal Drug Evaluation

Ruby Singh, Ph. D
Silvia Piñeiro, Ph. D

phone 240-276-8209 fax 240-276-8118
phone 240-276-8227 fax 240-276-8118