Stakeholder Input at Antimicrobial Resistance: USDA Planning Workshop

May 15, 2011

I. Current antibiotic use and resistance monitoring

A. Gaps

1. Metrics
   a) Metrics for defining goals, end points, or defining success
      (1) To what level are we trying to reduce antibiotic resistance?
   b) Metrics for relating how antibiotic resistance in animals impacts public health
   c) Metrics for triggers on when to take action

2. Data
   a) Lack of data on the rates of antibiotic drug use and resistance in animals and people pre and post banning of antibiotics in animals
      (1) Lack of antibiotic drug use data
         (a) Standardized, user-friendly data on drug use by food animal species including label/extra-label use, method of administration, indications for use, quantities being used, prevalence of animal diseases for which drugs are being used (including defined triggers for taking action)
         (b) Data to refine prudent use guidelines to better inform clinical decision-making and manage resistance transfer (umbrellas several items)
      (2) Lack of antibiotic resistance data
         (a) Standardized, user-friendly antibiotic resistance data by food animal species/microorganism/antibiotic (including defined triggers for taking action)
(b) Data on human illnesses and outbreaks resulting from antibiotic resistant and susceptible bacteria that is put into perspective in regards to incidence rate in defined populations

(c) Data for Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee to establish additional clinical breakpoints

b) Ecology

(1) Lack of data to understand the impact that drug use in animals has on antibiotic resistance development in food animals and the impact that resulting antibiotic resistance has on human health

(2) Lack of understanding of virulence characteristics of antibiotic resistant and susceptible zoonoses and anthropozoonoses

c) Economic impact

(1) Lack of knowledge of the economic impact of proposed Food And Drug Administration changes to antibiotic use in food animals scheduled to take place in 3 years

d) Development of human resistance

(1) Lack of information on when exposure becomes infection as not all exposed become ill

(2) Lack of information on the contribution of antibiotic use in animals to human health

(3) Lack of understanding on whether changes in agriculture would impact human health

3. Communication

a) Lack of understanding of non-governmental stakeholders (consumers, producers, etc.) on roles of different agencies and how they function together to address antibiotic resistance issues

b) Lack of common understanding of terminology that leads to confusion and disagreement:

(1) Terms used to define the purpose of drug use (therapeutic use versus prevention versus control versus growth promotion)
The term “trend” appears to be being used to support taking action without a common understanding of its meaning.

Lack of common understanding of how data will be interpreted

c) Gap in consumer knowledge of risks from preparation and consumption of raw animal products

4. Funding

a) Lack of funding to address gaps

B. Suggested Activities to Fill Gaps

1. Develop metrics.

a) Clearly define endpoint the agencies are seeking to achieve to:

(1) Improve chances for achieving the endpoint; and

(2) Obtain stakeholder support for achieving the goal.

2. Evaluate the entire farm-to-fork continuum through study of the microbiome. Populations of microorganisms can shift for a variety of reasons and if the reasons are not accurately identified, the problems cannot be mitigated. Microorganisms need to be followed at various points in the process.

a) Consider tracking microbial ecology instead of conducting isolated research projects. The relevance of differences in sampling consistently over time versus random sampling needs to be examined. Realistic estimates of antibiotic use need to be related to antibiotic resistance and is difficult for periodic studies to demonstrate the relationship.

b) Consider a Collaboration in Animal Health and Food Safety Epidemiology (CAHFSE)-type program to track microorganisms longitudinally while evaluating antibiotic use and management practices.

c) Improve understanding of transfer of resistance genes.

d) Evaluate the persistence of microbes on farms and products in markets.

3. Conduct Risk analysis.

4. Consider antibiotic resistance as a One Health issue.

a) Evaluate any lessons learned from Denmark and Europe on the ban of growth promotion for changes on impact on human health.
b) Review human illness cases to determine where exposure occurred.

c) Look for transfer from animals to humans as well as humans to animals.

5. Strengthen the National Antibiotic Resistance Monitoring System (NARMS) and National Animal Health Monitoring System (NAHMS).

a) The USDA function within NARMS needs more funding support. But before funding it as is, clarify the questions NARMS is trying to answer and determine the appropriate samples to collect and the appropriate locations to collect them.

b) Provide standardized, user-friendly access of NARMS data to the public with a continuous improvement of turn-around time of data.

c) Consider NARMS and NAHMS as research functions rather than regulatory functions.

d) Monitor total microbial populations to include susceptible and resistant pathogens.

e) Determine the appropriate microbes to study.

f) Establish the integrity of sampling strategies that are currently not representative.

g) Match human monitoring to animal monitoring and include non-enteric species.

h) Increase the frequency of NAHMS studies.

i) Collect and report empirical data from NARMS.

6. Conduct Research

a) Have the USDA develop a longer term, strategic research agenda to which industry and academia and government could all contribute.

   (1) The Agricultural Research Service and National Institute of Food and Agriculture are well positioned to conduct and coordinate research efforts.

b) Pose the right questions to appropriately design research and to provide accurate context for data. For example, sales data are being used as a proxy for how much antibiotics are being used on farms, which may not be accurate.
c) Re-invigorate a focus on agriculture in universities so that the next generation of researchers and scientists will have an agricultural base of knowledge.

d) Have graduate students contribute to research, data gathering, surveillance support, addressing globally induced challenges, and looking at use of rapid growth technologies.

e) Prioritize microbes for study.

f) Prioritize enteric microbes and non-enteric microbes causing concerns for human health regardless of whether or not they come from animals.

g) Address the issues of population growth and needs for increased production through data gathering, research, and surveillance.

h) Evaluate real time detection of pathogens to allow for pre-transport testing for strategic slaughter

7. Engage stakeholder support to fulfill surveillance data needs through joint initiatives.

a) Engage stakeholder support.

(1) Industry is willing to participate in studies if the results are aggregated and confidentiality is ensured. Industry and USDA should first collect and provide data on antibiotic use and animal management practices on farms. The 2008 Farm Bill may help secure confidentiality for volunteers.

   (a) Slaughter establishments could provide data on antibiotic resistance patterns.

(2) The National Cattlemen’s Beef Association is interested in:

   (a) Providing info/insight into the operation of the industry and to be a conduit to provide accurate information into various segments of the industry; and

   (b) Assisting USDA in program design, collection, analysis reporting and outreach to members.

(3) The Infectious Disease Society of America (IDSA)

   (a) Can advocate for an agriculture coalition for support to agencies;

   (b) Suggests obtaining congressional funding;
(c) Will work with membership to support enhanced human surveillance by the CDC.

(4) Consumer advocacy groups can work with individuals impacted by antibiotic resistant infections.

(5) Academia is:

(a) Positioned for basic research and technology development; and

(b) Positioned to work both on-farm with producers and in-plant with processors, and can shift direction quickly.

8. Refer to past work.

a) Codex Risk Analysis Guidance 77

b) NARMS Strategic Plan and other NARMS-related information such as input given at public meetings

c) General principles on judicious antibiotic use in humans and animals

d) FDA Guidance 152 and other documents as an example of important drugs for human medicine to determine most important drug/bug/species to study

e) Draft Guidance 213 (CVM)

f) Veterinary Feed Directive (addresses medically important antibiotic use in food animals)

g) FDA Draft Guidance 213

h) FDA Guidance 209

9. Evaluate the economic impact of antibiotic resistance issues.

a) Evaluate human health costs.

b) Evaluate production costs.

c) Evaluate international sales and accessibility of product by evaluating the experience of other countries such as Denmark.

10. Evaluate the international impact of antibiotic resistance issues.

a) Evaluate trade policy impacts.

11. Conduct outreach and education.
a) Educate consumers on the risks of preparing and consuming raw animal products.

b) Develop materials to address changes in demographics.

c) Disseminate information and educate through extension services.

II. Management practices to reduce antibiotic resistance

A. Gaps

1. Metrics

   a) Lack of outcomes being measured for different management practices

   b) Lack of data on links between effectiveness of management practices to address pathogens and human health outcomes

2. Data

   a) Lack of understanding of advantages and disadvantages of different management practices by species to reduce use of antibiotics (such as stocking densities, grazing, and organic production)

      (1) Lack of data at preharvest due to short life cycle for poultry

      (2) Lack of understanding on extent to which antibiotic treatment at parent/grandparent flock stages affect human health outcomes

      (3) Lack of understanding of effective management practices during challenge times for different commodities such as neonatal and weaning times for dairy

      (4) Lack of understanding of the impact of certain management practices such as withdrawal of antibiotic drug use for growth promotion in Europe

      (5) Lack of understanding of impacts on resistance from changes to feed

   b) Lack of technologies to immediately detect pathogens of interest on live animals, carcasses, final products to make decisions.

   c) Lack of understanding of the nature of pathogen loads going into the plant with or without the use of antibiotics.
There is a need to determine whether the level of pathogens on products impact public health risk.

There is a need to determine if there are differences in public health risk from antibiotic susceptible versus resistant pathogens.

d) Lack of understanding of the impact of probiotics, prebiotics, and feedstuffs on microbial ecology

e) Lack of understanding on how the use of interventions on the farm changes what translates to what is found at slaughter

f) Lack of understanding of the relationship between exposure and infection

g) Lack of understanding of the selective factors for resistance (what factors beyond use cause resistance to persist, such as co-selection)

h) Lack of understanding of post-harvest interventions and how these impact resistance

B. Suggested Activities to Fill Gaps

1. Develop metrics with goals in mind.
   a) Conduct experiments and research funded by the federal government in support of a clear, strategic, unified research agenda.
   b) Prioritize antibiotic resistance issues in human health whether or not there is an animal link.

2. Provide timely information on key animal health issues by food animal species for which antibiotics are being used and the key times food animal species are being treated.
   a) Conduct more frequent NAHMS-type studies.
   b) Evaluate individual animal diseases to inform management practices in addition to any systems approach.
   c) Link practices in quality assurance programs with outcomes for continuous improvement.

3. Conduct research.
   a) Find better ways to evaluate effective management practices because of the difficulty in detecting small changes in management practices (confounders).
(1) Measure how different producers manage risk (large production facilities versus small)

b) Evaluate how to optimize antibiotic regimens to minimize selection for resistance to improve prudent use.

c) Evaluate molecular characteristics identified on farm and compare to what is found in infected people.

d) Aim on finding ways to prevent instead of treat disease.

e) Evaluate the utility of antibiotic residue data for informing antibiotic use practices.

f) Improve the efficiencies of new technologies and interventions.

g) Assure coordination and harmonization with international standards.

4. Inform stakeholders of risk management choices.

a) Develop tools to mitigate risk.

b) Develop a menu of tools for stakeholders to help them manage risk (example: Integrated Pest Management).

5. Coordinate intergovernmental efforts to facilitate development of interventions.

a) Decrease the time lag for approving intervention strategies.

b) Have a common understanding between USDA and FDA regarding intervention strategies such as irradiation.

c) Improve the efficiency of the approval process for new technologies and interventions.

d) Support Innovation Veterinary (IVET) FDA that is working to develop guidance for regulating alternatives to antibiotics.

III. Alternatives to antibiotics to treat and prevent diseases or to enhance production in food animals

Alternatives to antibiotics (compounds that decrease the need for antibiotics) include (but are not limited to):

- Genetic identification of individuals more resistant to disease
- Novel vaccines, passive antibodies, hyperimmune serum
- Investigation into immune-enhancing products
- Animal-side diagnostics (rapid tests to select therapy or no therapy)
- Complementary and alternative veterinary medicine (CAVM) (e.g. botanicals)

A. Gaps

1. Lack of information on standard of evidence for showing benefit to producer, animal, and food safety
2. Lack of information on therapeutic equivalency of alternatives
3. Lack of information on cost effectiveness
4. Lack of data on antibiotic resistance development
5. Lack of information on pharmaceutical support
6. Lack of understanding of consumer acceptance of alternatives
7. Lack of information regarding economic feasibility of management practices
8. Lack of knowledge of the multitude of confounders that may affect evaluation of management practices (such as size of operations)
9. Lack of understanding and alignment of ongoing research

B. Suggested Activities to Fill Gaps

1. Develop metrics.
   a) Develop a global framework and a way for measuring success for future research.
   b) Examine evaluation tools and international models.
   c) Consider a HACCP model for evaluating alternatives.

2. Develop an overarching framework for research.
   a) Pursue preharvest strategies such as vaccines.
   b) Prioritize animal diseases for developing vaccines.
   c) Offer incentives to farmers to participate in research.
d) Take a granular approach to understanding alternatives, antibiotic use, animal health, and public health impacts.

e) Investigate protocols for examining alternatives.

f) Study any unintended effects of using alternatives.

g) Study the impact of comprehensive animal health preconditioning.

h) Study alternatives in factorial experiments.

i) Look for alternatives that do not impact gut microbes.

j) Explore whether and how alternatives reduce the use of antibiotics in animal agriculture.

3. Further research and partnerships on novel intervention strategies at postharvest to decrease microbial populations at slaughter.

4. Consider NARMS-like monitoring for assessing the impact of alternatives.

5. Evaluate the cost effectiveness of alternatives.

6. Show benefits and cost effectiveness of using alternatives to provide incentives for farmers to use them by determining:

   a) Availability of products,

   b) Ease of use,

   c) Applicability, and

   d) Cost effectiveness.

7. Consider possible tax incentives for development and commercialization of advances.

8. Consider incentives for the pharmaceutical industry to develop useful technologies.


   a) Communicate procedures to potential sponsors, researchers, manufacturers.

   b) Improve coordination of approval of alternatives between agencies.

   c) Develop approval processes for emerging technologies.

10. Improve communication regarding alternatives
a) Identify journals that will publish alternative medicine results (many will not, so it is difficult for communicating scientific, evidence-based information).

b) Conduct outreach through One Health programs to educate farmers on alternatives.

c) Facilitate constructive collaboration amongst stakeholders by defining terms and increasing understanding of issues.