

For the Record

Straight talk about antibiotic use in food-animal production
Volume 4, Issue 3

Sponsored by ALPHARMA Inc. Animal Health
August 2005

INSIGHTS ON THE ISSUE

Of the frantic, by the frantic, for the frantic

In early April, three activist groups and two medical associations together petitioned the Food and Drug Administration to immediately rescind approval for most antibiotics used for growth promotion in food animals. The coalition claimed seven classes of antibiotics in feed were no longer safe, not because the drugs had changed, but because FDA last year changed its policy regarding how drug makers should test the safety of their products.

If the primary rule of governing,

like medicine, should be to first do no harm, it's good news that FDA plods slowly into change based on administrative petitions such as this one. However, the change in FDA policy on considering the risk of human antibiotic resistance in an animal drug's approval has again opened the door for a widening of what's come to be known as "the precautionary principle." It's a political device designed and now typically used by environmental protectionists to turn the blunt instrument of government against

scientific outcomes that don't support their cause. Experience shows the precautionary principle ignores benefits of any practice like antibiotic feeding, and focuses on the possible risks — real and imagined — until risk becomes the sole driving issue.

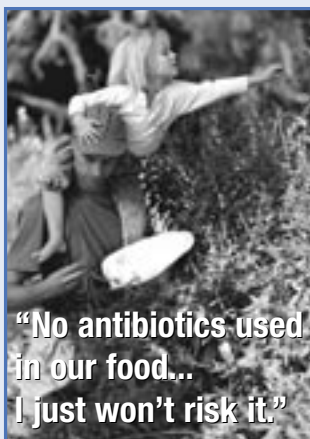
It's an issue needing some perspective, says the Animal Health Institute's Richard Carnevale: "The issue of resistance and its impact on human health is not one of possibility but, rather, probability."

Also in this issue:

- **Industry and regulators have worked together to incorporate risk assessment of antibiotic resistance into animal drug regulations. And their thanks? It's been turned against you by activists.**
- **When does healthy caution become stifling overprotection?**

A little perspective on risk

In lending the backing of the American Public Health Association to a ban on farmers' use of antibiotics, executive director Georges C. Benjamin noted, "Scientific studies have linked the overuse of antibiotics in animal feed to health risks in humans, including medical treatment failures that sometimes result in death." One study has estimated roughly a 1-in-250 million chance you could die from a case of *Campylobacter jejuni* that's resistant to one class of antibiotics, fluoroquinolones, which you might catch by eating contaminated ground beef. How does that theoretical risk compare to some of the other risks of being killed in a year's time?



"No antibiotics used in our food... I just won't risk it."

RELATIVELY HIGHER RISK OF...

Killed by fireworks	4 times more likely
Killed by your pajamas catching fire	11 times more likely
Killed by a dog	16 times more likely
Killed in an earthquake	27 times more likely
Dying of a bee sting	47 times more likely
Killed by lightning	57 times more likely
Killed by falling out the window	484 times more likely
Drowning in the swimming pool	552 times more likely
Dying in a plane crash	567 times more likely
Killed by gunfire	662 times more likely
Dying from complications of medical care	2,468 times more likely
Killed by being run over	5,288 times more likely
Killed in a car crash	14,284 times more likely

Source: S.A. Anderson, R.W. Yeaton, L.M. Crawford, "Risk assessment of the impact on human health of resistance *Campylobacter jejuni* from fluoroquinolone use in beef cattle," Food Control 12 (2001), 13-25. National Safety Council.

For the record

The safety and market-worthiness of any consumer product — cars, toys or antibiotics — have traditionally balanced their benefits against measurable, quantifiable risk. Now, some are fighting to change that standard to limit antibiotic uses they don't agree with for ideological reasons.

New guidance from FDA on resistance risk

When Environmental Defense filed its April FDA petition demanding an end to most feed-antibiotic use, it relied heavily for evidence on a handful of letters FDA recently sent to manufacturers of certain antibiotic feed additives. The letters, obtained by Freedom of Information Act request, were asking three drug makers to meet with FDA to discuss the agency's decision to classify their penicillin-based premixes as having a potentially high risk of contributing to penicillin resistance in human pathogens. It was the first look backward at previously approved drugs under a new FDA policy called Guidance for Industry 152 (GFI 152).

GFI 152, the result of five years and three versions worth of public comment and regulatory drafting, is the federal government's attempt to comprehensively address whether antibiotics used in food animals contributes to development of antimicrobial resistance against human drugs. Not a regulation with force of law, the guidance is instead an expla-

nation of FDA's "way of thinking" about how a drug's safety profile should include resistance issues. Drafted with input from both industry and activists, it explains a science-based process drug sponsors may use when they seek approval of a new drug for food animals — a process to demonstrate the drug will not create a risk for untreatable resistant bacteria in humans. The agency hopes it will help prevent antimicrobial drugs considered high risk from being used in food animals, which theoretically could make human drugs less effective. FDA has said the new guidelines will be used not only for new drug approvals, but will be used to reevaluate the risk of drugs that have already been on the market — many for decades.

Apparently not satisfied drugs weren't being hauled off the market in the year and half since FDA finalized GFI 152, Environmental Defense et al noted in their petition that although they recognized the provisions aren't mandatory, use

of the seven medically important classes of drugs in feed could now be presumed to be inconsistent with FDA's criteria for a safe drug.

How it's supposed to work

GFI 152 is known as a "qualitative methodology" — as opposed to quantitative — for assessing the risk of developing and spreading resistant germs and harming human health. Before starting the assessment, an overall drug profile is presented, including its structure, class, mechanism of action and known resistance patterns. Then, its importance to human medicine is analyzed to determine if its use in animals might select for resistance that might have human-health impact. The methodology sets out a three-part checklist for assessing a drug's safety, by considering the following:

Release. Can use of the antibiotic in question be expected to result in resistant bacteria in the animals? This assessment relies heavily on the assumption that the longer you use a drug, the more animals you use it on simultaneously, and the lower the level below the concentration that actually kills off germs, the greater likelihood resistance will develop.

Exposure. Is it likely humans will ingest those resistant bacteria? This aspect is based on per capita consumption of different meats and current levels of pathogens in those meats.

Consequence. What's the likelihood a doctor would have difficulty treating a person with an antimicrobial drug because the bacteria infecting the person had acquired resistance to the drug? This leg of the assessment weighs heavily on the fact that the animal drug or a member of the same drug class is the sole therapy or one of few alternatives.

GFI 152's methodology ranks all three of those risk aspects on

For the Record

For the Record, sponsored by a grant from ALPHARMA, is designed to help unite the industry and provide a unified, rational message on behalf of producers whose freedom to use safe, effective, economical production methods is at stake. Working together, we can set the record straight on antibiotics. Questions or comments? Contact Steve Kopperud at skopperud@poldir.com. Want to read past issues or link to more information on this issue? Visit us online at www.alpharma.com/ahd

Good drug, bad drug?

Under GFI 152, any drug deemed either "highly important" or "critically important" in treating human disease — based on whether that drug class is the sole therapy for resistant human disease or one of only a few alternatives — automatically disqualifies it for use on a herd-wide or flock-wide basis. According to the Environmental Defense petition, that means FDA shouldn't permit any use of seven drug classes as feed additives or water solubles delivered pen- or barn-wide.

WHAT WOULD GO...	WHAT WOULD BE LEFT...
<ul style="list-style-type: none"> • Penicillins • Streptogramins – Virginiamycin • Macrolides – Tylosin, Erythromycin, Oleandomycin, Tilmicosin • Lincosamides – Lincomycin • Sulfonamides – Sulfantran, Sulfadimethoxine, Sulfaquinoxoline • Tetracyclines – Chortetracycline, Oxytetracycline • Aminoglycosides – Spectinomycin 	<ul style="list-style-type: none"> • Bacitracin methylene disalicylate • Bacitracin zinc • Bambermycin • Tiamulin

a scale of low, medium or high, and then gives the drug an overall level of human health risk. If those assessments show that the risks are significant, FDA can deny its marketing approval. Barring that action, FDA could approve the drug, but limit how and where it's sold and used. Any drug categorized as high or medium risk has been deemed not "appropriate" for use as a growth promotant. As the Environmental Defense petition points out, that removes all but four of the drugs used for that purpose in swine.

More harm than good?

The Animal Health Institute, the trade organization representing animal drug makers, has dismissed this new petition as simply a resurrected attempt to get FDA to strike down antibiotic feed additives as a public health emergency, which the agency has declined to do to appease similar petitions in the past.

However, AHI and others have pointed out that regardless of this current petition's outcome, some issues remain about whether GFI 152 really makes a meaningful contribution to settling the risk issue. Consider the following:

■ Even FDA admits this "qualitative" approach isn't the only method a company could use to assess risk. In fact, it encourages companies to pursue others they find more appropriate. The seldom-spoken concession is that qualitative analysis is only second best to the hard numbers of quantitative assessment — second-best but acceptable nonetheless because requiring quantitative data would be so time-consuming, data-intensive and almost impossible to conduct on new compounds that few health products could ever meet the standard and successfully reach market.

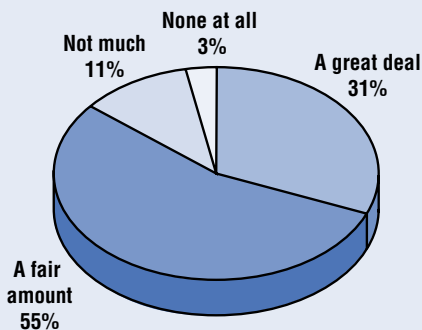
■ Guessing at the risk of exposure based solely on per-capita consumption of meat presents several problems which inflate the risk, including the fact that

What, we worry?

A survey conducted in summer 2004 by Ipsos Global Express found 47 percent of Americans said the food supply is as safe as it used to be; another 28 percent said it is safer. Consumers in Western Europe showed similar reliance on their food supply. A Gallup poll later that same summer found 31 percent of Americans expressed "a great deal" of confidence in government's ability to ensure a safe food supply. That's an increase from only 19 percent in July 2002, Gallup said.

"How much confidence do you have in the federal government to ensure the safety of the U.S. food supply?"

Source: Gallup Poll News Service.



although meat samples are tested for resistant organisms while raw, not much gets eaten in that form.

■ The consequence aspect draws no distinction between the importance of antibiotic resistance in food-borne bacteria and antibiotic resistance in bacteria people catch by other means, such as by nurses and medical workers who don't wash their hands between patients. Little to no connection has yet to be drawn between the use of an antibiotic in livestock and the development of resistance in a human organism that doesn't come from those animals. Yet GFI 152 rates those risks equally.

■ GFI 152 completely ignores the potential risks in not using antibiotics on the farm. Applied mathematician and risk-assessment expert Tony Cox — who has just published a new textbook on this subject — has developed quantitative mathematical models that show, for instance, the human health risks from continued use of macrolides, the antibiotic class that includes erythromycin, are typically on the order of less than one excess case per year. In contrast, his model shows continued use of those antibiotics in animals may actually prevent more than 1,000 human cases per year. If

that quantitative analysis is even approximately correct, Cox says, restricting animal antibiotic use is actually doing more harm than good, by increasing the need to use human antibiotics and hastening the development of resistance. Sound, data-driven, quantitative risk assessment — even if we don't have complete data — trumps good intentions and qualitative labels that are ultimately aimed only at getting everybody to agree by making the labels so soft as to be impossible to disagree with.

The end game?

In earlier public input on GFI 152 as it was being written, the coordinator for the activist group Keep Antibiotics Working lamented that a complete review of all current drugs under the framework "might take decades." It should come as little surprise, then, that this latest petition was filed the same week legislation was introduced — for the third congressional session in a row — to effectively outlaw low-level antibiotic feeding. That legislation would give FDA two years to satisfy concerns continued use does not contribute to antibiotic resistance affecting humans, and failing that, would ban them.

For the record

Consumers don't seem to be buying activist rhetoric that somehow eating meat poses a risk.

We should focus on making better decisions

For the record

The bad news is when you choose to omit crucial quantitative information in ranking risks, the value of that information in making meaningful decisions declines.

From my perspective as a professional risk analyst, qualitative risk-rating systems that only use labels such as “High,” “Medium,” and “Low” to rate risks and their components are inherently limited. Under natural conditions, qualitative risk assessment necessarily makes rating errors and can produce high ratings even for very small risks. Because that built-in high error rate makes their results untrustworthy, in many practical cases it makes their value for improving risk-management decisions zero.



Tony Cox, President
Cox Associates
Denver, Colo.

Any ranking process that is intended to serve the needs of rational decision making should not rank drugs and problems, but should rank potential solutions to those problems.

What does that type of useful, rational decision making require?

Risk evaluation requires numbers

First, it requires identifying risk management alternatives. For example, should we continue to use a drug? Should we ban it? Should we wait and see? Should we restrict it? Simply rating the importance of an antibiotic doesn't necessarily answer those questions.

My favorite example is the use of fluoroquinolones. There's a risk assessment that looked at the risks of continuing to use fluoroquinolones, but it never considered the risks of banning fluoroquinolones. Our work at Cox Associates has estimated that the risk from increased disease that would follow banning fluoroquinolones from use in chickens is at least two orders of magnitude larger than the risks from continuing to use them.

Secondly, rational decision making requires assessing the probable human health consequences of each decision option and, of course, picking the one that has the most desirable probable consequences.

The bad news is that risk is inherently quantitative. When you choose to omit crucial quantitative information from a risk-ranking process, the value of that information for decision making decreases. For many current qualitative ranking systems, a problem could be rated as “important” whether one person in a million years is affected or a million people in one year are affected. But that basic numerical information makes a huge difference in impacts.

I've said many times that the *quantitative extents* of exposure, release and consequence constitute essential information. Ignoring these leads to poor risk assessments and poor decisions. FDA's current system requires those who would use it to come up with subjective beliefs and ratings for events that are not even clearly defined, using vague ratings that are also not clearly or coherently defined. And those ratings are used to suggest risk management actions without regard to how they compare to alternative solutions or how they affect probable human consequences — in many cases contrary to common sense. That combination tends to give very strange risk rankings.

Could actually cause more disease

Augmenting or replacing purely qualitative ratings with simple, robust quantitative variables and rating functions usually resolves the inherent shortcomings of purely qualitative approaches, even when the inputs are only imprecisely known. For example, we have developed a new quantitative Rapid Risk Rating Technique, or RRRT, which helps make meaningful risk predictions and supports more effective risk-management decisions.

In applying RRRT to estimate the human health impacts from terminating virginiamycin use in animals, we estimated that at least an additional 6,660 human campylobacteriosis cases per year are likely to occur. That compares to at most 0.27 additional streptogramin-resistant vancomycin-resistant *Enterococcus faecium* infections in human patients likely to result from its continued use. So, even though a lack of complete information precludes a deterministic conclusion, clearly it appears very probable that a withdrawal of virginiamycin would cause many times more human illnesses than it would prevent.

FDA should develop an approach to managing antibiotic use that allows us to reap the benefits of these drugs while maximizing their effectiveness. Antibiotics in animal husbandry benefit the public in several ways. They can reduce the cost of meat and the numbers of infective microbes in food. People are healthier as a result. Effective policy-making cannot be based on logic that attributes blame for rising resistance to relatively minor use of antibiotics in animals while neglecting the far more likely cause represented by increasing use in humans.

Tony Cox is author of numerous risk-assessment studies and the upcoming Quantitative Health Risk Analysis Methods: Modeling the Human Health Impacts of Antibiotics Used in Food Animals.