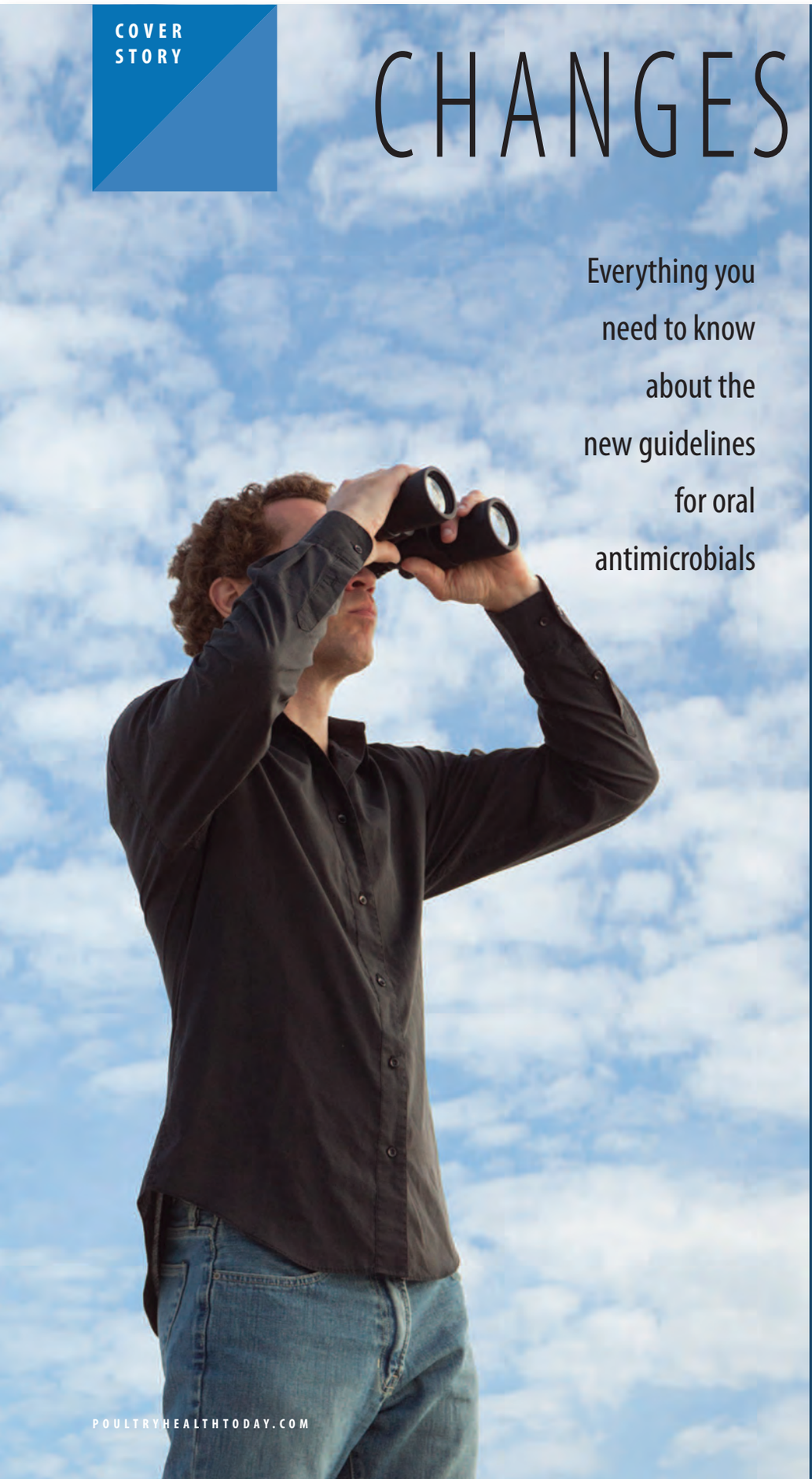
POULTRY HEALTH TODAY

COVER STORY

CHANGES AHEAD

Everything you need to know about the new guidelines for oral antimicrobials



The US poultry industry has already shown that it knows how to use antimicrobials judiciously.

Whether the goal is to preserve the effectiveness of the limited tools available, to simply reduce feed costs or to avoid having poultry meat products rejected by vigilant government inspectors, poultry producers have ample incentives to abide by the rules and make every dose count. Using anything excessively or needlessly simply doesn't pay.

So what impact will FDA's new usage guidelines have on your production practices, the health and performance of your birds and perceptions of health-minded yet cost-conscious customers?

In this special report, *Poultry Health Today* editors take an in-depth look at what FDA calls Guidance for Industry No. 213 — the rationale behind it and the changes in store for the US poultry industry.

The nuts and bolts of GFI No. 213

FDA recently rolled out new guidelines for antimicrobial usage in poultry and livestock — not just how the medications are categorized and prescribed but also how, when and why they should be administered in the field.

The two documents, officially known as Guidance for Industry (GFI) No. 213 and a proposed Veterinary Feed Directive (VFD) regulation, aim to help producers, veterinarians and pharmaceutical companies use antimicrobials in ways that, according to FDA, address public health concerns while maintaining the health, performance and welfare of poultry and livestock.

Although GFI 213 is written primarily for drug "sponsors" — those companies that own the right to market the drug — the content of the document will inevitably affect everyday management practices for veterinarians and producers. The updated VFD regulation is intended to simplify and streamline the existing process for veterinarians to authorize the use of certain animal drugs in feed.

For the good of the industry, everyone is being encouraged to play by the rules or, in this case, the FDA's strongly recommended guidelines.

What FDA wants

More than anything, FDA wants the poultry and livestock industry to think twice before orally administering any antimicrobial drugs that have been deemed "medically important" to humans.

In other words, any drugs that are considered important for treating infections in people — penicillins, tetracyclines, fluroquinolones and macrolides, to name a few — should be used sparingly in animal feed and water and only to target specific diseases or organisms.

FDA also wants producers to consult with veterinarians before using any medically important drugs.

Under the new guidelines, for instance, producers should first get a confirmed diagnosis and a veterinary prescription or a VFD from a licensed veterinarian before running any of these medically important medications through the birds' drinking water or feed.

A VFD is a written form issued by a licensed veterinarian authorizing the use of certain drugs in feed for a specific reason and time period. This document

So you know

Antibiotics are substances produced by a microorganism that kill or prevent the growth of another microorganism. Antibiotics are antimicrobials, but antimicrobials also may be synthetic compounds.

is provided to both the feed mill and the producer (see sidebar).

In addition, FDA wants medically important drugs administered in feed and water to be limited to the treatment, control and prevention of disease. The agency acknowledges that improved growth and feed efficiency might be secondary benefits of maintaining healthier birds, but using medically important antimicrobials solely for production benefits is not considered a judicious use of such drugs under the new guidelines. FDA is also urging drug companies to remove performance claims from all medically important antibiotics within 3 years of GFI 213's adoption.

Notable exceptions

There are two notable exceptions to the new FDA guidelines that poultry producers and veterinarians need to understand.

First, the new FDA recommendations do not apply to synthetic anticoccidials or ionophores used in feed to prevent or control coccidiosis — the costly, parasitic disease that threatens the health and welfare of all chickens. These compounds

Guidelines at a Glance

- **Antimicrobial drugs that FDA has deemed medically important to humans should be used in poultry and livestock only to prevent, control or treat a specific disease or organism.**

- **A Veterinary Feed Directive (VFD) should be obtained from a licensed veterinarian before using any feeds containing medically important antibiotics; a veterinary prescription is required for medically important water medications.**

- **Medically important antibiotics should not be used solely for performance benefits, such as improved weight gain or feed conversion.**

- **Only those antibiotics not medically important to humans with approved FDA claims for increased growth rate and improved feed conversion should be used to optimize performance.**

- **Synthetic anticoccidials, ionophores and antibiotics not considered medically important to humans may be used without a VFD, though veterinary involvement is still encouraged for all antibiotic decisions.**

- **The new FDA guidelines are voluntary, but the agency plans to monitor industry progress and decide in 3 years if more action is required.**

are not considered medically important to humans and are used almost exclusively in poultry and livestock. No special paperwork is needed to obtain or use these products.

The other exception is any group of feed antibiotics that FDA does not consider medically important to humans. In poultry, this would include antibiotics in the bacitracin and bambermycins families (see sidebar).

That means poultry products like bacitracin methylene disalicylate (BMD®) can still be used without a VFD to prevent or control necrotic enteritis, another omnipresent and potentially deadly gut disease of poultry, although veterinary involvement with any antibiotic is still recommended. When used at 50 g per ton of feed — coincidentally, the same level routinely used to prevent necrotic enteritis — BMD can still be used for "increased rate of weight gain and improved feed efficiency," which result from the antibiotic's ability to preserve the integrity of the gut wall, helping to ensure the absorption of nutrients from feed.[1] Flavomycin 4 (bambermycins) is another poultry feed medication that can be used without a VFD to aid feed conversion and growth rate.

Previously approved combinations of anticoccidials, ionophores, bacitracins and other non-medically important drugs also may be used according to label directions without a VFD.

3-year phase-in

While complying with the new FDA guidelines will be voluntary for drug sponsors, the agency says it will monitor the pharmaceutical industry's progress for 3 years before determining if further action is needed.

"FDA believes a proactive and collaborative strategy is the best approach to ensuring judicious drug use, as this provides a path forward for addressing public concerns [about on-farm antibiotic usage] in a manner that takes into account animal-health needs and the impact on animal agriculture," said William T. Flynn, DVM, MS, deputy director for science policy at FDA's Center for Veterinary Medicine.

Speaking at an antibiotic forum held last year at the International Production & Processing Expo, he added, "Antibiotics have historically played an important role in animal agriculture. Being responsive to the concerns being raised is critical to preserving the continued availability of these important tools."

In a word

The new guidelines for antimicrobials suggest limiting the use of medically important antimicrobials to one or more of these specific uses:

1 TREATMENT

Administered only to animals exhibiting clinical signs of disease.

What's a VFD?

The phrase Veterinary Feed Directive (VFD) may be new to poultry veterinarians and producers, but the process has actually been around since 1996, when Congress passed the Animal Drug Availability Act.

VFDs were developed by FDA to help the agency get a better handle on the use of certain new, therapeutic antimicrobial medications used in feed, primarily to reduce the rate at which resistance develops and thereby prolong medication's effectiveness.

PUTTING IT IN WRITING

Previously, VFD only applied to new feed antibiotics. Any over-the-counter (OTC) feed antibiotics registered before 1996 were grandfathered in under old rules.

Once pharmaceutical companies remove production claims from medically important antibiotics, thereby placing them under VFD status, veterinarians will need to issue a VFD authorizing their use.

Basically, the VFD is a written statement that lets producers obtain and use certain drugs in poultry or livestock feed in accordance with the FDA-approved directions for use. VFD drugs must be used under veterinary supervision and in compliance with the drug's FDA-approved label.

SPECIAL RELATIONSHIPS

The VFD process is pretty straightforward. In the past, a licensed veterinarian — one with a "valid veterinarian-client-patient relationship," as the FDA calls it — visited the farm, assessed the situation and determined whether use of a VFD drug was warranted. If the drug were needed, the veterinarian would issue a signed VFD order.

Under the new guidelines, FDA has relaxed some administrative procedures with the goal of easing the shift from current OTC status to the new VFD umbrella. For example, rather than use a government definition on a veterinarian-client-patient relationship, the agency is deferring to AVMA practice standards — criteria that licensed practitioners use anyway — for defining relationships between veterinarians and their clients.

For more information on the new procedures, visit fda.gov and search for Veterinary Feed Directive.

In FDA's Dec. 11 announcement, Flynn added, "We need to be selective about the drugs we use in animals and when we use them. Antimicrobial resistance may not be completely preventable, but we need to do what we can to slow it down."

Want to learn more?

For more information on the new FDA antimicrobial guidelines, visit poultryhealthtoday.com or go to fda.gov and search for GFI 213.

[1] Miller SH, Skinner J, Davis SW. Efficacy of Probiotic and/or BMD® in the Feed for Control of Necrotic Enteritis Caused by *Clostridium perfringens* in Broiler Chickens. Zoetis Global Poultry. Data on file.

2 CONTROL

Administered to a group of animals when a portion of the animals in the group exhibits clinical signs of disease.

3 PREVENTION

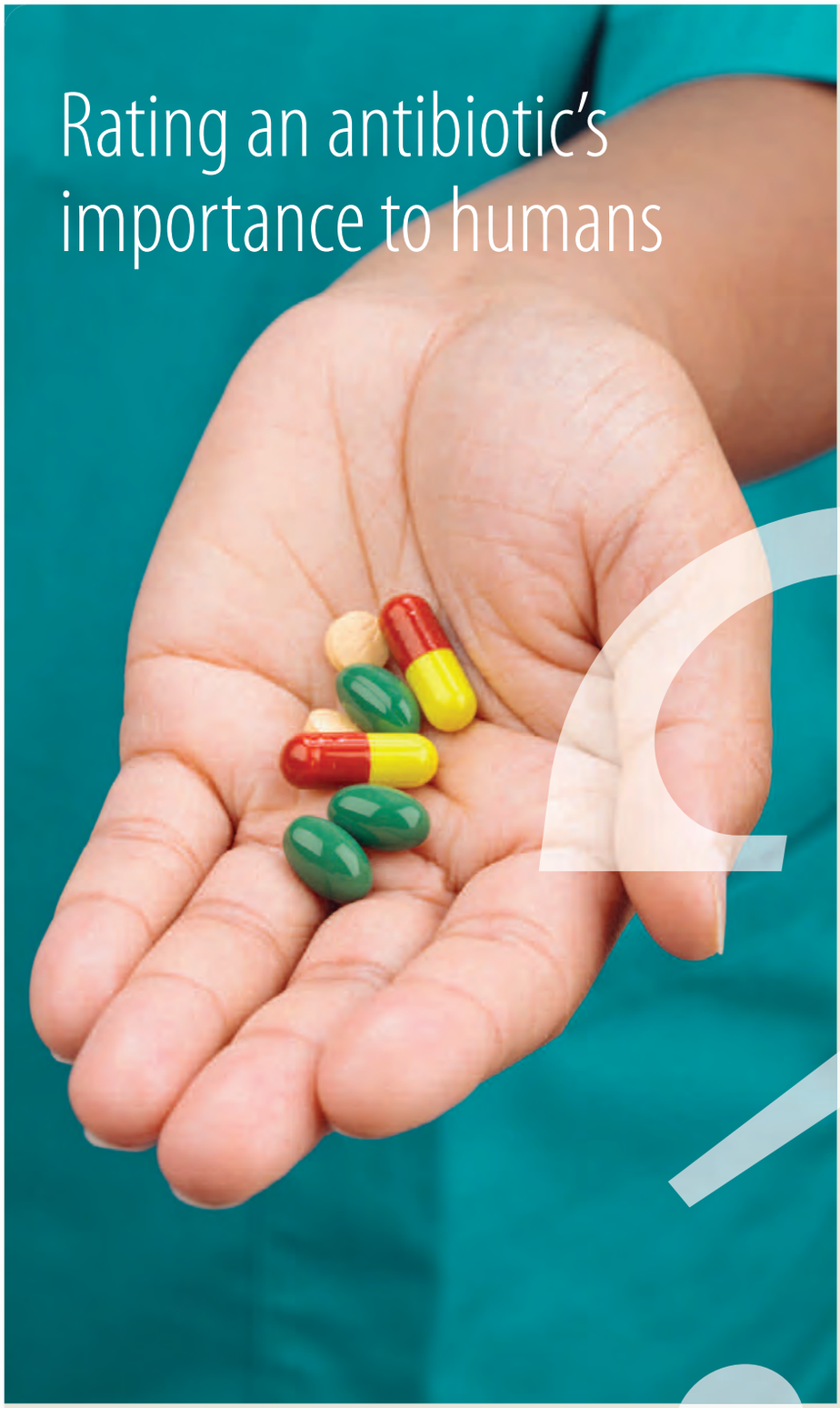
Administered to a group of animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.

Producers are urged to refrain from using medically important antibiotics to enhance performance. Likewise, drug manufacturers are being asked to drop performance claims from the labels of these antibiotics.

Only non-medically important antibiotics with established, FDA-approved performance claims could be used for increasing growth rate and feed conversion.

POULTRY HEALTH TODAY

Rating an antibiotic's importance to humans



How does FDA determine which antibiotics are medically important to humans?

Basically, the agency asks five questions about each antibiotic:

1. **Is it used to treat enteric pathogens that cause foodborne disease?**
2. **Is it the sole therapy or one of few alternatives to treat serious human disease or a drug that is an essential component among many antimicrobials in treatment of human disease?**
3. **Is it used to treat enteric pathogens in non-foodborne disease?**
4. **Is there cross-resistance within the drug class or linked resistance with other drug classes?**
5. **How easily does resistance to a drug cross over to other genera and species of organisms?**

Table 1 Poultry antimicrobials and their importance to human medicine, according to FDA*

IMPORTANT	HIGHLY IMPORTANT	CRITICALLY IMPORTANT
Cephalosporins, 1st generation	Aminoglycosides	Cephalosporins, 3rd generation
Cephalosporins, 2nd generation	Aminopenicillins	Flouroquinolones
Cephamycins	Antipseudomonal penicillins	Macrolides
Monobactams	Carbapenems	Trimethoprim/sulfa
Quinolones	Cephalosporins, 4th generation	
	Chloramphenicol	
	Clindamycin	
	Glycopeptides	
	Isoniazid	
	Metronidazile	
	Natural penicillins	
	Oxazolidones	
	Penase-resistant penicillins	
	Polymyxin B	
	Pyrazinamide	
	Rifamycins	
	Streptogramins	
	Tetracyclines	

* List of medically important drugs will be reviewed periodically and updated by FDA as needed.[2]
Source: Zoetis, based on GFI #152, Appendix A[3]

MAKING THE GRADE

If the answer to questions 1 and 2 is yes, the antimicrobial is considered "critically important." If either question draws a nod, the antimicrobial is considered "highly important."

If the answer to questions 1 and 2 is no, but yes to questions 3, 4 or 5, the antimicrobial is rated "important" to human health. All other antimicrobials are considered non-medically important.

Under the new guidelines, producers will be advised to obtain a VFD order before any medically important antibiotics are used in poultry, and then these antimicrobials should only be used to prevent, control or treat a disease indicated on the product label.

Table 1 lists FDA's current rankings of commonly used poultry antimicrobials. FDA insists the list is "not static," however, and that it will periodically be updated as necessary, taking into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans or changes in US prescribing practices.

[2] Source: GFI #213
[3] Source: GFI #152

WILLIAM FLYNN

WHY COMPLY?

FDA's new antimicrobial guidelines are strictly voluntary — to a degree. In the agency's own words, they "do not establish legally enforceable responsibilities"; they merely "describe the FDA's current thinking on a topic" and, unless otherwise indicated, should be viewed only as recommendations.

However, pharmaceutical companies that choose to comply with GFI 213 would effectively give up currently approved performance claims on antibiotics deemed medically important and place the remaining therapeutic uses under veterinary oversight — essentially making them prescription or Veterinary Feed Directive products instead of over the counter. Once that happens, veterinarians and animal producers cannot use these drugs for increased growth or feed efficiency.

So what incentives do drug sponsors have to comply?

Apparently plenty. Over the 3-year period following the release of the final version of GFI 213, FDA plans to evaluate the rate of adoption of its proposed changes. If it thinks the process needs a boost, it "will consider further action as warranted."

In the meantime, the agency says it "recognizes the significance of the proposed changes" on the animal pharmaceutical industry, producers, the feed industry and veterinarians. It, therefore, opted for a voluntary phase-in to get everyone on board with its new direction.

'RIGHT WAY TO GO'

"We are very optimistic that the industry will work cooperatively with us," William Flynn, deputy director for FDA's Center of Veterinary Medicine, told *Poultry Health Today* in a recent interview.

"We think this is the right way to go and it's important to make progress. And that's why we have set some fairly specific goals and timelines in connection with this."

Even so, Flynn insisted it would not be a "completely open-ended" process. "We're going to have to reassess where we are as we work through the voluntary process. We feel pretty confident, based on the interactions we've had with the industry, that this will be a successful approach and will have a high degree of cooperation.

"But again, we'll have to re-evaluate at the end of [3 years] and make a determination if we need to take any other steps."

MEASURING SUCCESS

How will success be measured? There are many yardsticks available, but one clear indicator to Flynn will be the pace at which manufacturers drop performance claims — such as an increased rate of growth and feed efficiency — from the medically important antibiotics.

Under the new guidelines, performance claims and over-the-counter availability will be limited to antimicrobials not considered medically important.

POULTRY HEALTH TODAY

How do antibiotics promote growth?

Under the new FDA guidelines, in-feed antibiotics with FDA-approved performance claims can still be used to promote growth and improve feed efficiency — as long as they are not considered "medically important" to humans.

That's good news for efficiency-minded poultry producers looking to meet escalating world demand for healthy, safe and affordable chicken and turkey. Still, the words "growth promotion" and the role these antibiotics play in poultry production are often misinterpreted by those outside of production.

For example, one non-medically important poultry antibiotic that will retain its FDA-approved performance claims is bacitracin methylene disalicylate (BMD®). The product is indicated for "increased rate of weight gain and improved feed efficiency" in both broilers and turkeys when used at the rate of up to 50 g per ton of feed. Coincidentally, BMD is also labeled for broilers at the rate of 50 g per ton for the prevention of necrotic enteritis caused or complicated by *Clostridium* spp. and other organisms susceptible to the product's active ingredient.

'BIT OF A MISNOMER'

That begs the question, does the antibiotic simply make birds grow — or is improved performance really secondary to improved health that enables birds to reach their full genetic potential?

"The term growth promotion in itself is accurate but may be a bit of a misnomer," says Steven Clark, DVM, senior poultry technical services veterinarian, Zoetis Inc.

For a long time, it has been thought that subtherapeutic doses of in-feed antibiotics enhance growth by modifying intestinal microflora, although exactly how isn't known for sure and is still up for discussion, he says.

Explanations have included a reduction in subclinical infection, decreased production of microbial products that have toxic effects, depressed microbial competition within the bird for nutrients and enhanced absorption, according to the Poultry Science Association.[1]

CHANGES IN MICROFLORA

As far back as 1992, investigators from the University of California-Davis conducted studies indicating that feeding antibiotics may permit growth by preventing immunologic stress and associated metabolic changes.[2]

Another theory emerged in 2007 with publication of a paper entitled "The Nonantibiotic Anti-Inflammatory Effect of Antimicrobial Growth Promoters, the Real Mode of Action? A Hypothesis." The author argued that most antibiotics have a non-antibiotic, anti-inflammatory effect, which may in turn reduce wasted energy and spare it for production.

"Concomitant or subsequent changes in microflora are most likely the consequence of an altered condition of the intestinal wall," Professor Theo A. Niewold, PhD, of the

"THE TERM GROWTH PROMOTION IN ITSELF IS ACCURATE BUT MAY BE A BIT OF A MISNOMER." Steven Clark, DVM

Catholic University, Leuven, Belgium, wrote in *Poultry Science*.[3]

This theory would also explain why results with so-called growth-promoting antibiotics are highly reproducible, as opposed to those obtained by antibiotic alternatives that are aimed at microflora management, Niewold wrote.

BENEFIT TO FLOCK HEALTH

However they work, their benefits are well known to those involved in poultry production.

"Today, we know that one of the primary mechanisms of action these antibiotics have in poultry is preventing subclinical necrotic enteritis caused by *Clostridium perfringens*," says Charles Hofacre, DVM, MAM, PhD, University of Georgia.

"A flock of chickens is like a city of 25,000 people," he told *Poultry Health Today*. "Someone is always going to be sick or getting sick. Not all birds in a flock may need to be treated with an antibiotic, but there is always a percentage of them that get the benefit of the drug because of low-grade intestinal illness."

This is particularly evident in flocks that for one reason or another are experiencing greater stress and, as a result, a greater disruption in their intestinal bacterial flora.

"In these flocks, we will see a bigger benefit from the use of an antibiotic at the minimum necessary dosage for prevention of subclinical or clinical necrotic enteritis," Hofacre says.

Clark agrees that antibiotics with performance claims are especially helpful for flocks in stressful situations, provided they are used judiciously. "If the birds run out of feed or the birds don't eat as well for whatever reason, they're under stress and efforts to stabilize the situation by improving intestinal health can be helpful," he says.

Hofacre and Clark see other secondary benefits from their use. By improving feed efficiency, consumers get the same amount of meat without requiring as much corn and soybeans for growth. That means more grain for other uses, Hofacre says.

"And if chickens can be grown more efficiently with less feed," Clark adds, "there's less manure output and less impact on the environment."

[1] Poultry Science Association. Newly proposed mechanism for the action of antimicrobial growth promoters (AGPs) may open the door to the development of new non-antibiotic alternatives to AGPs. Press release, 2007. http://www.poultryscience.org/pr032607.asp

[2] Roura E, et al. Prevention of immunologic stress contributes to the growth-permitting ability of dietary antibiotics in chicks. J. Nutr. 1992;122:2383-2390.

[3] Niewold TA. The nonantibiotics anti-inflammatory effect of antimicrobial growth promoters, the real mode of action? A hypothesis. Poult. Sci. April 2007 vol. 86 no. 4.

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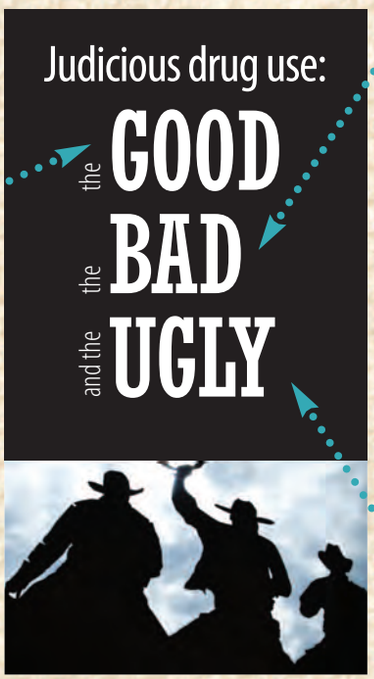
Charles Hofacre, DVM, MAM, PhD

POULTRY HEALTH TODAY

According to FDA, judicious use means administering an antimicrobial drug appropriately — and only when necessary.

After comparing notes with a few poultry veterinarians, *Poultry Health Today* editors borrowed the title from an early Clint Eastwood film to rate a few possible real-world scenarios:



the GOOD

- Using approved antibiotics in the feed or water to treat clinically sick birds, control the spread of a diagnosed disease or prevent commonly occurring, highly prevalent diseases like coccidiosis or necrotic enteritis.
- Administering a non-medically important antibiotic with documented performance benefits to preserve the gut wall of broiler chickens and optimize nutrient absorption, growth potential and feed utilization.

the BAD

- Using a medically important antimicrobial without veterinary consultation or a VFD order.
- Using any antimicrobial — medically important or otherwise — for a purpose or duration not indicated on the product's label.

and the UGLY

- Using valuable medically important drugs solely for the purpose of promoting growth or improving feed efficiency.
- Giving medically important drugs to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease.