

**Animal Health Institute
Capitol Hill Antibiotics Briefing
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Thank you Ron and it is a pleasure for me to be here today. As you know and as Ron mentioned there has been an awful lot of talk about antibiotics used in agriculture and unfortunately invariably a lot of the comments that we hear from the media and others is that there is not very much control over antibiotic use, bio producers and veterinarians, but in fact, that is not true. There is a lot of control and it begins with the FDA approval process. What I'd like to do today is give you a little bit of an overview of how FDA does that and also touch on some of the other layers of protection that Mr. Phillips talked about before I turn it over to the experts in our companies that are actually involved in day – to – day decisions and data development on new antibiotic products.

This slide gives you just sort of an overview of how animal health, as a matter of fact, how human health products are developed. First of all there is a discovery phase and that is a very difficult phase because as it is mentioned here about 1 out of 20,000 discoveries are successful. I would say with antibiotics the ratio is probably even lower, that that number is with all pharmaceuticals, so it's a very difficult process to find a compound that works and bring that through the development process to an actual product that 's used in animal or in human medicine. Then of course we have preliminary trials, pre clinical trials, which involves a lot of acute toxicity and product dose and product testing, clinical trials which are the ones that prove the product is effective in a clinical setting and is also safe for the patient and then we have an FDA regulatory review, which takes all of that data and looks at it and decides whether the product should be improved, so then the product is finally approved and with animal drugs it's kind of unique because all those approvals are published in the Federal Register as opposed to human medicine. That is a unique feature of animal drugs, so every day you can look at the Federal Register and see what might be approved because FDA has put a notice in there telling you all about it.

And then there is monitoring and this slide talks about adverse reactions, but there is a lot more than adverse reactions that are monitored after the drug is approved, in particular antibiotics and I'll get into that a little bit. That whole process we have estimated takes between 7 and 10 years and up to 100 million dollars depending on the product. Obviously it's more expensive to get approvals in food animals, cattle in particular than it is companion animals, but it can that expensive, so it's a very time consuming expensive process.

Just to go over antibiotics specifically there are four uses of antibiotics that have traditionally been approved by the FDA. Those are disease treatment, which we all recognize as an animal gets sick and we give short term therapy to high doses to try to get it over that disease. There is disease prevention, which is very important in herd and flock management of bacterial infections. There is disease control and that would be sometimes termed metaphylactic

treatment where there has been an outbreak in a herd or flock and to stem that type of infection you go in there with antibiotics to try to control the other animals from getting sick and then there is the growth or health maintenance and that is the claims that are on some of these labels for weight gain and feed efficiency. Obviously that is a subject of a lot of controversy these days. AHI recommends about – suggests about 13% of all antibiotics are used for growth promotion and feed efficiency, the rest being therapeutic and I say therapeutic because disease treatment prevention and control are all considered therapeutic by the AVMA, the American Veterinary Medical Association, the FDA and Codex Alimentarius, which is the international food standards organization under the UN.

The FDA approval process involves every aspect of the drug from safety to efficacy to quality and under safety that is safety to the animal. Tests have to be run to determine that the drug can be used safely in the animal. There is environmental safety. There is an environmental assessment that must be done for all drugs. In some cases it is more extensive than others as you could imagine, but environmental safety has to be assured and then there is human food safety and that is a very rigorous and expensive area in the review process and that involves with antibiotics three separate evaluations if you will. One is for residues, residues that might end up in meat or poultry products are looked at by FDA for potential toxic effects and there are safe levels set, which are called tolerances by FDA, but in the rest of the world they're maximum residue limits and that is termed used in Codex Alimentarius.

There is also impacts on gut flora. What does that mean? Well that is what if you were to eat residues in food and that could affect the intestinal, the normal intestinal bacteria in your intestinal tract. They run studies to determine whether there is any adverse effects from the potential level of residues in the meat and they use that in conjunction with the toxicology data to set the MRL, so that is another aspect of the antibiotic approval process that is specific to antibiotics that impact on gut flora. That can be fairly time consuming as well. And then finally, you've all heard of Guidance for Industry 152. That is the FDA guidance document that came out in I think 2002 and Scott Brown will be talking about that in much more detail. That has to do with looking at resistance and the potential impact of a resistant bacteria that might be on meat, not residue, but resistance bacteria that might be on meat that a consumer might consume and then potentially have a human health problem.

So that is the FDA approval process in a nutshell. This sort of emphasizes again the antibiotic regulation, how stringent it is, human safety, animal safety, environmental safety. Quality, manufacturing standards are very rigorous. Good manufacturing requirements under FDA laws are very, very expensive to comply with and so that can be a major part of the application and efficacy. Efficacy testing is required for any claim that is on the label. FDA requires adequate and well controlled studies as it's taken out of the Food and Drug and Cosmetic Act to prove that the drug is – If it's labeled for any of these claims, disease treatment, disease control, prevention or health maintenance are safe and effective and so this is a rather rigorous approval process that must be present. I will mention the health maintenance. We talk a lot about growth promotion. There hasn't been a product approved for – an antibiotic approved for growth promotion in probably over 20 years, so the drugs we're talking about are old. They've been out there a long time. There really is nothing new approved for that use.

This gives you an idea of the different kinds of products that are available and are approved by FDA. Injections of course, we're all familiar with those in individual animal treatment. There can be water medications, which is a common way to medicate poultry and then there is feed additives and a bag of feed additive you can see, which is an antibiotic. It can be added to feed that we've been talking about a lot lately. FDA regulates every aspect of the label including the species that are on there, the use within the species, sometimes the sub species or sub form of livestock within that species, the dosage, the uses directions and cautions. The FDA reviews every aspect of that label and it is a very detailed evaluation. I would mention that according to the extra label use provisions in the law there are some provisions for an antibiotic to be used, extra labeling, but it can only be used by directed by a veterinarian for the therapeutic purposes under a valid veterinary client patient relationship and they only use animal approved and FDA approved animal and human drugs, so that is a specific provision that we go on that would be applied to any antibiotic that is used and again, it's only therapeutic. In feed there is no extra label use allowed, so you hear a lot about the uncontrolled use of feed, believe me, it's not uncontrolled because antibiotics cannot be used extra label. It can only be used according to the label directions on the package.

Again, Scott will get into this a little bit more, but an overview of the FDA risk assessment that they go through with Guidance 152 again issued in 2002. It requires manufacturers to evaluate new and existing products based on risk assessment and that assessment is basically three components, release, how likely the bacteria is to be selected by use of the drug, exposure, what is the likelihood of people being exposed to these bacteria in the food supply and then what is the consequence, what could happen if an antibiotic – if antibiotic resistance was selected for it in the animal and it got through to people. So again, Scott will get into that a lot more in detail.

I would like to mention that and FDA has elaborated on this in their recent Guidance 209 that they just published. It's applicable mainly to new products that have limited or no veterinary use. Why is that? Because there are built risk management restrictions based on the final categorization of the risk, so while it is very useful for new products it's not as applicable for existing products that have many years of market experience, a lot more data available, for example the NARMS data, the antibiotic resistance data that is available out there. So the – and the extent of use on a lot of these feed additives don't conform to some of these predetermined restrictions, so a company evaluating a product for market will know what those restrictions are in 152 and will tailor their product to meet those restrictions, so in resistant feed additives it's not as easy to apply 152 because as I said it's more restrictive therefore we think assessment through a quantitative means which Dr. Shryock will get into is probably a better way to evaluate the safety of those products. Post approval layers of protection beyond the FDA approval process, of course we have the U.S.D.A. National Residue Program. They test for a variety of antibiotic residues in meat and poultry to determine compliance with the FDA withdrawal times. Antibiotics are a big focus of the NRP, which not only monitors across slaughter plants for national prevalence, but conducts in plant testing, so for example, there might be a particular class of animals that have shown a particular high violation rate. Dairy cattle come to mind. They will set up in plant programs to evaluate dairy cattle for residue, so it's not only across a national incidence, but it's detailed in plant testing as well, a fairly

elaborate program. NARMS, of course that is the National Antibiotic Microbial Resistance Monitoring System, which was set up about 10 years ago for antibiotic resistant bacteria in foods mainly focused on salmonella and campylobacter. It's got three arms, the FDA retail meat survey, which has been in operation less time than the other two arms and it's the smaller in nature, the USDA Animal Carcass and Processed Meat Program, which is mainly done in slaughter plants and other processing plants and CDC monitors isolates from human infections that present themselves to public health laboratories.

The USDA pathogen, HACCP and Pathogen Reduction Regulation called the Mega – reg, which went into place about 10 years ago was intended to set up certain hygienic standards for meat plants to operate under. At the time they also set up standards for salmonella in particular. Now they've most recently established a standard for campylobacter, which was a lot harder to do, but for years they have been monitoring the salmonella contamination of plants and poultry plants through that standard. Of course resistance bacteria could be part of the salmonella – that salmonella campylobacter contamination, but as I'll show you in a minute it ends up being a very small subset of that, so any action to affect the prevalence or the presence of bacteria in meat and poultry will of course reduce resistant bacteria as well. For example, salmonella standards for chickens, the latest U.S.D.A. baseline studies show that about 7 ½% of carcasses had salmonella finding. It doesn't mean it had an infectious dose of salmonella, but they did find some bacteria on those carcasses. Now that has gone down over the years. When they first started pathogen reduction it was about 20% of all chickens you could find salmonella on, so they had a really good success rate with reducing the incidence of salmonella in chickens.

So if you take that 7 ½% and you look at NARMS and take a look at some of the critical antibiotics that come out of the NARMS program if you picked up cephalosporin, there are three cephalosporins, which are monitored at NARMS, they range anywhere from .4 to 15% prevalence, so therefore you might speak theoretically that less than or equal to one parts in a hundred might have resistant salmonella on it. Again, not an infectious dose, it might have it. So again, try to put in context it's a fraction of the bacteria that are there and the bacteria that are there have gone down. With fluoroquinolones, which you know as ciprofloxacin there were 0% and the same with Trimetropin Sulfa was 0%. Why did I pick out those three antibiotics? Those are identified as critically important antibiotics in the FDA Guidance 152. It gives you an idea of looking at the total contamination on the carcass versus what might be there from a resistant nature.

Finally, judicious guidelines, the ADMA has prepared those guides for all species groups. They are endorsed by FDA. CDC has a program called Get Smart on the Farm, which instructs on more optimal antibiotic use and there are producer quality assurance programs that help to instruct how to use antibiotics, so all of that also helps to make sure that antibiotics are being used safely and effectively on the farm.

Before I turn it over to my two colleagues to get into more details about what I said I just wanted to bring up one issue and this is with regard to antibiotic volumes. We at AHI continually meter 70% of all antibiotics that are used in the food animals for non therapeutic purposes. I just wanted to take this opportunity to try to correct that record. That statement seems to be

embedded in stone. Every reporter uses it and it's derived from the 2000 Union of Concerned Scientists "Hogging It" report. Unfortunately, when we talk about 70% of antibiotics people think those are all human antibiotics. Well they're not. In fact, in the UCS report and our own AHI data 45% or more of that usage is – are with drugs that have no use in human beings and therefore they can't really cause resistance problems, so you got to take that 70% and put it in context with what actually is the reality, so if you take that 45% away from the 70 you don't have nearly the antibiotic uses of human antibiotics in animals that the 70% would lead you to believe. Unfortunately, you'll see numbers from Denmark and other countries that show the US has a much higher antibiotic volume. Well those other countries aren't including the ionophores and our [INAUDIBLE] and mainly those ionophores are being used for a parasite, not an antibiotic. They're being used to treat coccidiosis, which is a big problem in chicken, so there is a lot used in chicken, but again, no human use, so I just want to put that in context because it's really bothered us that that number keeps getting floated out there and we just want to make sure people understand where it came from.