

**Animal Health Institute
Capitol Hill Antibiotics Briefing
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It's a privilege to be here. I really appreciate the opportunity to tell you all a little bit about what we do in the pharmaceutical industry. The job that I have is overseeing a number of people who are involved with assessing essentially the safety of the products that we develop. We are a part of Pfizer Human Health, the largest pharmaceutical company in the world. Pfizer Animal Health is a very small component of that and we are in close interaction with the toxicologists and the people who are involved with the pharmacology and the metabolism of other medicines. I would like you to put in context that we as a United States of America have about 300 million or so people, but in that same country we have nearly a billion, billion chickens, nearly a 100 million beef cattle and calves, about 64 million pigs, 8 million cats, 74 million dogs and then a number of dairy cattle as well, so as you can see we have a large population of animals in the United States and we need to be involved with making sure that they are healthy animals and if they're in the – and, or the food supply that those healthy animals translate to healthy food as well. Now lest you forget, human medicine – human disease and animal diseases are very closely related. About two – thirds of the human pathogens that are found come from animals. There is a link between animal health and human health and that is the premise by which my company and the AHJ work is that there is a close link between the two.

No I don't want you to think that bacterial diseases or diseases that are treated by antibiotics constitute a large fraction of that. In fact, of the 1,400 human pathogens the vast majority are viruses, protozoa or parasites that antimicrobial or antibacterial agents are not effective or nor should they be used. I'll give you some context. Epidemics in the last say nearly 20 years of nearly all of them, 11 out of the last 12 are the result of zoonotic disease. There is clearly a link between human health and animal health. Difficulties, there is a balancing act. There is a strong agreement among experts that for one health we need to be thinking about the development of medicines for humans and animals. We need to think about the appropriate or judicious use of medicines in both humans and animals and we need to have that monitoring system that Dr. Carnevale talked about so that once medicines are out on the market that we can be monitoring what is happening as a result of that. In veterinary medicine and the approval process just as in human medicine there is what is called pharmacal vigilance, which is looking at approved products and seeing whether there are adverse events that are a lot larger than we expected, whether there are significant and severe adverse events. Part of pharmacal vigilance or keeping vigil on what is happening is the National Antimicrobial Resistance Monitoring System, that collaborative effort that Dr. Carnevale talked about. It's a critical aspect that while not perfect is a good place for us to have data with which we can make good solid science based decisions.

For most of us we come from a pharmaceutical company that is devoted to human health and as I just mentioned human health and animal health are closely related, so very clearly the animal health industry believes that animal health and human health are linked, but human health is

clearly out in front. We're not gonna sacrifice human health for animal health. In fact, we believe that human health is enhanced by animal health. Enhancing the health of animals enhances the safety of the food supply and that is an important component as we are developing medicines for animals.

As Dr. Carnevale mentioned the regulatory process is time consuming. It's costly and aspects of efficacy or how effective the product is in the intended species is a part of it. The quality of a product, which is essentially it has to be the same quality as that approved for human medicine. Then safety for the intended species, we have to make sure that it is safe for the cattle or the swine or the chickens. We have to conduct environmental assessments because we know that there are – there is a concern about what is happening in the environment and every medicine that we develop in animals goes through an environmental assessment to assure that there is no significant affects on the environment. We have to be sure that this product is safe for those who are administering the product. Very few animals self medicate. There is always a person involved and we have to be sure that the products are safe for those who are administering the products.

The department we're here to talk about today is human food safety. Both are traditional components of toxicology and the residues of those medicines in the edible tissues of animals, but for the purposes of this discussion today focusing on two components that are specific to the approval of antibiotics in animals. One is the microbial safety risk assessment, trying to understand what components are critical for the transmission of resistance and whether there is a significant concern there and secondly, whether the residues in the edible products alter the gut flora in human beings who consume those edible products as a part of the daily diet.

We'll fund this principally on Guidance 152 and how we assess that and I'm bringing it from the standpoint of a company that is working on new products, new medicines for animals as well as new indications or new claims for existing medicines and that is where Guidance 152 is principally focused is those new medicines for animals that have not yet been approved and for those new indications and new claims for existing medicines. It is designed as a qualitative risk assessment and I guess I should back up just for a moment and make sure that I clarity that risk is – has two components. It has one component, which is hazard, and one component that is exposure. Now if I can bring it to you in kind of a clear understanding if you think about getting hit by lightening there is clearly a hazard about getting hit by lightening. We hear about people who are hit by lightening and the consequences of that, but if there are no thunderstorms there is no risk and so the exposure and the hazard have to come together to really understand what is the risk of an adverse occurrence happening. That is what this is all about and because it's a new medicine or new indication in many instances there are not data out there that can be used to quantitate the risk and so for that prime reason these are set up as qualitative risk assessments and it is composed of three different parts. One is a release assessment. One is the exposure assessment and one is the consequence assessment. I'll talk about each one of them more thoroughly as we go on. The release assessment essentially helps you understand what is the risk that resistant bacteria will develop in the animals that have been treated with the medicine. The exposure assessment assesses whether those resistant bacteria can transfer from the animals to the food supply and the consequence assessment says what is the concern that

those resistant bacteria in the food supply are going to cause a medical concern, a medical consequence in human beings that consume that foodstuff. The three of those together come together for an overall risk assessment and FDA can take some actions based upon that. They can deny the approval of the product or they can label the product with certain restrictions and we'll talk about those in a few minutes.

The release assessment is what we as a pharmaceutical company generate data to support or to understand. It consists of what is the mechanism of activity of the antimicrobial. How does it work? What does it do at the bacterial level? We also need to understand what is the spectrum of activity. Is this an antibiotic that is treating the diseases in the animals and but more importantly what is the activity against those zoonotic organisms that are of concern that can be found in the food supply? What is the pharmacokinetics or what is the disposition of the medicine in the animals? Where does it go? How long does it stay there? How is it cleared from the animal and those sorts of things? That is part of pharmacokinetics. Pharmacodynamics has more to do with once it's in the animal what is its affects on the bacteria? A little less of an in vitro kind of approach and more about what is it doing at the bacterial level in the animal. Resistance mechanisms have to be understood. How does resistance develop in new organisms that we're concerned about? Is it a traditional style of resistance? Is it one that is new or novel or is it one that has already been demonstrated previously? What about the transfer of resistance from one bacterial species to another? How does that occur? To what extent does that occur? All of those kind of things have to be understood. What is the selection pressure? Is there a concern and what is the level of concern that using this antibiotic in animals can actually produce a pressure on bacteria that have resistance or have susceptibility? What is that pressure? Is that a normal pressure or is that a significantly different pressure? What about mutation frequency? Does the mutation of a bacteria increase as a result of being exposed to the antibiotic or not? There are several other factors as well that are involved. Clearly it's looking at a number of pieces that are involved here, each one of which can be assessed as a high, medium or low risk assessment. Through that there is an overall assessment for release of whether the risk is high, medium or low.

The next step is the exposure assessment and the best way to describe this is it's sort of a combination of what is the quantity or amount of that commodity consumed and what is the contamination rate of the particular bacteria of concern on that commodity? So as an example in this case let's just assume that it's poultry consumption. Poultry would be considered to be high consumption because we eat a lot of poultry in the United States. Salmonella contamination might initially have been considered high although as new data are generated and as passive procedures are implemented and show an improvement in the contamination rates these exposure assessments may change and so as Dr. Carnevale mentioned while previously was at 20% salmonella carriage in carcasses is now 7 ½%. As those procedures at slaughter houses improve and the contamination rates go down these exposure assessments obviously would change as well. These are not data that a pharmaceutical company will generate, but we will look at the literature. We'll look at what U.S.D.A. provides. We'll look at what other sources of information that are out there to understand and to be able to provide an assessment of exposure of transfer of the resistant bacteria from animals to human beings.

The consequence assessment is a little bit of a different one. This is a categorization of the classes of antimicrobials based upon human medical need and it's determined as critically important, highly important or important. This categorization was done through the advisory panel, the Antibiotic Advisory Panel, the Center for Drug Evaluation Research of FDA. That is the side that evaluates human medicines and they designated categories – sorry, classes of antibiotics as critically important, highly important or important based upon the importance to human medicine. I think this emphasizes that FDA Center for Veterinary Medicine is not looking at this in isolation, but rather they're working with their counterparts in human medicine to understand and to assess what the consequences are of different antibiotics being used on animals. You might ask how does that consequence assessment get determined. There are two criteria that the Center for Drug Evaluation and Research Advisory Committee used. One is, is that class of antibiotic used to treat enteric pathogens in food borne disease? Is it used to treat salmonellosis or campylobacteriosis in human medicine and is it essential and perhaps sole therapy for a specific serious human disease? If the class of antibiotics fulfill both of those categories it would be considered to be critically important. If it fulfilled only one of those two classes or categorizations it would be considered highly important and if it fulfilled neither one of those it would be considered an important antibiotic and so as an example ionophores have fulfilled neither one of these criteria in human medicine, so they would be considered to be in the important categorization, but not critically or highly important.

As you pull this all back together you can see that each one of those has a qualitative assessment, highly interloped and through that there is a matrix that comes up with the overall risk estimation. One important point to recognize is that if a class of antibiotics has been judged as critically important that by default gives you a high risk estimation overall irrespective of whether the release assessment or the exposure assessment was considered to be high, medium or low. Now that essentially is providing an extra degree of conservatism or precaution into this guidance and what it means is if your class of antibiotic falls into those – the critically important class then the mitigating steps that the FDA can take are really falling into that what it can do for critically important antibiotics. Now again, FDA can take one action of saying, no, we're not going to approve the product. It can also take the steps of saying, no, this is only a product that can be by prescription only. They can declare that there is no extra label drug use and that there will be a ban on extra label drug use. There can be a no prevention use, so instead of having therapeutic uses that are treatment controlled and prevention it can choose that – to limit it to the therapeutic or therapeutic and control and it can even say no flock or herd use, only individual use. It can limit the method of administration to say this is only going to be by injection and you will not be able to use this in an oral medication fashion.

Last, but certainly not least, they can call for a Veterinary Medicine Advisory Committee hearing to determine with a body of experts from human and animal health whether this particular usage in this particular class of antibiotics should be approved for the uses intended and there have been two or three of those Veterinary Medicine Advisory Committee reviews of critically important antibiotics.

So how do companies use Guidance 152? Well first and foremost it was very helpful for us to have a guidance. Before Guidance 152 there was an assessment by the FDA Center for

Veterinary Medicine on microbial safety, but it was not clear what that assessment was. There was no structure to it. It was essentially kind of a black box that we didn't really understand. As the guidance has gotten approved and we're better able to understand it we can use it as an early default assessment as we're looking at new products and new indications. Does the new product or the new medicine concept, is the new indication fit with Guidance 152? What hurdles would be expected if it falls into a particular categorization? What are the hurdles that we might expect to have to fulfill to assure that there is microbial safety? Based upon those two things we might choose to pursue that particular new medicine or new indication or we might choose to divert those research funds and look at something else and develop something else.

We have had – I'll talk about this. We have had all of those situations that have occurred. The place where this is really helpful then is to use this Guidance 152 as a template for what studies are required, what data collection is necessary, how we should essentially design the dossier to submit to FDA Center for Veterinary Medicine for their review. We will often times seek concurrence on whether the approaches we're using to try to answer questions are the way that the agency believes it needs to be and certainly once we provide the data the agency reviews the data, provides their own interpretations and makes their own judgments.

So you might ask the question have any of these particular scenarios occurred. Has there been any instance where a company has chosen not to pursue a product or an indication because of microbial safety? That answer is yes, personal experience. Has a company chosen to pursue a product or indication and go on through the process and ultimately the agency came back and said, no, we don't believe that your assessment was appropriate or complete? Yes. Has a company chosen to pursue a new medicine or a new indication, gone through the FDA, CBM review process for microbial safety assessment and the agency said yes, we believe you have satisfied the assessment and we believe there is microbial safety? That answer is also yes, personal experience on all three, so the system is able to handle and make the decisions along the way for new medicines and new indications on existing medicines.

So I'd like to close just to remind you that contrary to popular belief veterinarians don't have that many options for treating diseases. There are literally hundreds of antibiotics approved for use in human medicine. There is probably a tenth of those that are approved for use in veterinary medicine. That means that there are not many arrows in the veterinarians quiver to use against infectious disease. The responsibility for developing new antibiotics is important both to human and animal health and a regulatory pathway needs to remain transparent and science based as it is today. Guidance 152 has helped us as an industry understand how the agency is going to formulate through safety assessments and provides that framework upon which we can design and implement our research program to develop the data that shows microbial safety. If we don't have that then we'll probably invest our R&D dollars in other areas with the consequences that veterinarians are gonna have even fewer medicines to use in the future and that would potentially compromise the animal health that contributes to human health.