KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

www.KeepAntibioticsWorking.com

October 28, 2014

Mike Taylor
Deputy Commissioner for Foods and Veterinary Medicine
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Misleading Promotion of Animal Drugs

Deputy Commissioner Taylor:

We, the members of the Keep Antibiotics Working (KAW) coalition, are writing to follow up with you on our concerns about promotional materials that illegally encourage the extra-label use of medically important antimicrobials for production purposes (i.e. growth promotion, feed efficiency, and improved performance). This follows on our May 14, 2014 letter to you, our meeting with you in person on July 2, and our July 25 letter to you. Despite FDA statements that the agency understands our concerns about this type of promotion and repeated FDA statements that growth promotion uses will be illegal after a company removes a production claims from the label, Novartis continues to promote the growth benefits of its tiamulin (Denagard) plus chlortetracycline combination and has even reversed changes made after we first raised the issue.

Since our meeting with you in July, KAW has reviewed both untitled letters and warning letters sent by FDA to drug companies. The misleading statements on the Novartis website are no less misleading than the statements in promotional materials that FDA has routinely challenged, yet we still have not seen any evidence that FDA has asked Novartis to remove the misleading information from its marketing materials.

Novartis's promotional materials are still misleading.

Although we discussed this at length in our meeting of July 2, we feel it is important to reiterate the specific concerns we have with the Novartis website and promotional materials.

1) The promotional materials are misleading because they claim that the product can be used for a much broader range of indications (including but not limited to claims that Denagard plus chlortetracycline can be used to improve production) than is on the approved label.

Denagard plus chlortetracycline is approved to treat (not control or prevent) "bacterial enteritis caused by Escherichia coli and Salmonella choleraesuis," and "bacterial pneumonia caused by Pasteurella multocida." The combination is also approved to control swine dysentery associated with Brachyspira hyodysenteriae. It has no approval for prevention of respiratory disease and the only approval related to respiratory disease is for treatment of Pasteurella multocida. Treatment refers to administration of a drug to a clinically ill patient which is different than disease prevention, the inhibition of "the introduction of disease into an area, herd, or individual[1]."

Despite the very limited range of approved indications, the Novartis website and promotional materials repeatedly refer to controlling subclinical respiratory and enteric disease. The Denagard website makes the following statements that combine both disease prevention and production claims:

> Even at subclinical levels, respiratory and enteric diseases can inhibit pig health, limiting performance and profitability. At times of health challenges in a grow-finish unit, Denagard® (tiamulin hydrogen fumarate) plus chlortetracycline (CTC) allows pigs to achieve and maintain better performance by controlling the disease challenges they face.
>
> Research results have shown that controlling respiratory and enteric disease with an in-feed antimicrobial regimen of Denagard plus CTC resulted in better growth and overall performance in grow-finish pigs.

Denagard plus chlortetracycline is not approved for controlling any respiratory disease and has only a single approval for controlling enteric disease, i.e. swine dysentery. It has

[1] http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UCM390290.pdf

no approval for production benefits. The use of this drug for the control/prevention of any indication other than swine dysentery would be extra-label use which is illegal for medications administered in feed. By emphasizing the production benefits and ignoring all animal health benefits (reduced morbidity and mortality) from the use of Denagard plus chlortetracycline, it is clear that Novartis believes producers are more likely to purchase this product for production benefits rather than approved therapeutic purposes.

2) The promotional materials are misleading because they fail to reveal important material facts about Denagard plus chlortetracycline (i.e. the approved indications for the combination are never communicated).

   The Novartis page promoting the production benefits of Denagard plus chlortetracycline does not provide a link to the approved label for this or any other Denagard containing product. The text describing Denagard plus chlortetracycline never mentions the indications for which this combination is approved. The fine print at the bottom of the page does list pathogens, but fails to distinguish between this and other approved products containing Denagard and also fails to distinguish between treatment indications and control indications. We assume this is to hide the very restricted number of indications for which the combination is approved in contrast to the recommendation in the materials that it can be used broadly for generic prevention of respiratory and enteric disease.

3) The Novartis promotional materials for Denagard and chlortetracycline are misleading because they make claims (production benefits result from controlling disease) that are not supported by substantial evidence.

   The webpage and associated materials assert that by controlling generic respiratory and enteric disease for which Denagard plus chlortetracycline has no approval, producers will receive the production benefits of better growth, improved feed to gain ration, and better overall performance.

   Novartis' website does not include the actual studies on which it bases these production claims, but KAW was able to find the study referred to for the growth claim. This study by Hammer provides no evidence that growth benefits result from controlling swine

dysentery[2]. In fact, it provides no evidence that the growth benefits shown were linked to any disease process whatsoever. The studies provided by Novartis on the website similarly provide no evidence that performance gains result from the therapeutic indications for which the drug is approved. None of the studies provide evidence that the treated animal's health was affected by swine dysentery, Salmonella, Escherichia coli, or Pasteurella multocida. Since both Denagard and chlortetracycline have been approved for growth promotion in swine, it is likely that the production benefits shown in these studies resulted from the poorly understood mechanism of growth promotion which is unrelated to the approved therapeutic indications.

4) The Novartis promotional materials are misleading because they omit important risk information (i.e. medicated feeds containing chlortetracycline should be used for no more than 14 days). While some of the limitations on the use of Denagard plus chlortetracycline are listed under cautions and warnings, the website and promotional materials fail to include the important restriction that the product be used for no more than 14 days. This restriction is on all feed medications containing chlortetracycline and we believe this use restriction is linked to the human food safety conditions under which chlortetracyclines are approved for use in feed.

   KAW believes that this omission like the failure to disclose the approved indications for Denagard plus chlortetracycline and the suggestion that the combination will provide production benefits is aimed at encouraging much broader use than would occur if the approved label were followed.

FDA has regularly contested promotional materials that have provided similar types of misleading information.

As discussed above and in our previous conversations the misleading material on the Novartis website is clearly aimed at encouraging the broad use of Denagard plus chlortetracycline for purposes including production purposes that go significantly beyond its approved indications. FDA has routinely challenged promotional materials for making claims like these in untitled and warning letters.

[2] http://orbit.dtu.dk/fedora/objects/orbit:63423/datastreams/file_5574380/content

FDA has regularly asked companies to modify promotional materials that claim that a product is effective for a broader range of indications than are described in the approved labeling. For example, FDA sent a letter on April 2, 2014 to AB Science asking that the company modify promotional materials on its tumor treatment product Kinavet-CA1 ® (masitinib mesylate) because the materials suggest that the drug "is effective for a broader range of indications than are described in the approved labeling." FDA sent a similar letter to Intervet on October 16, 2012 asking that the company modify promotional materials on the veterinary antibiotic orbafloxacin that "broaden the indications." In asserting that Denagard plus chlortetracycline is effective for "controlling" generic respiratory and enteric disease despite having a very limited control claim for swine dysentery, this promotional material is similarly misleading.

FDA has also challenged promotional materials that omit important material facts. For example, on August 2, 2013 FDA wrote to ECO Animal Health asking the company to modify promotional materials about the company's antibiotic drug Aivlosin® because they "fail to reveal material facts" about the approved indication. The promotional materials omitted the fact that the drug is to be used only in buildings where a disease outbreak has occurred. The Novartis materials omit much more by failing to ever state the approved indications for the Denagard plus chlortetracycline combination.

FDA regularly asks companies to modify promotional materials that make effectiveness claims that are not supported by substantial evidence. For example, FDA sent on March 10, 2014 a letter to Merck Animal Health asking that the company modify promotional materials for the antibiotic Zuprevo ™ that make "unsubstantiated effectiveness claims" including the claim that this drug which is approved for respiratory disease treatment and control can also be used to prevent respiratory disease. FDA also challenged Merck Animal Health on April 9, 2012 for making the unsubstantiated claim that the antibiotic product Resflor Gold® is more "fast acting" and "long acting" than shown by evidence.

The Novartis materials state that production benefits from Denagard plus chlortetracycline occur due to the mechanism of controlling disease. As discussed above the studies referenced do not show that these benefits result from approved therapeutic indications so there is no substantial evidence linking production benefits to the therapeutic action of the drugs. Despite decades of

research, the mechanism of growth promotion is still unclear[3], so it is unlikely that production benefits for drugs such as Denagard and chlortetracycline can honestly be attributed to the therapeutic benefits of their use.

FDA routinely challenges drug makers that omit risk information and most of the letters referred to above ask companies to modify promotional materials because of this type of omission. The restriction that feed additives containing chlortetracycline be used for up to 14 days is an important condition for the safe use of Denagard plus chlortetracycline that Novartis omits in the promotional materials.

Conclusion

KAW hopes that this additional clarification of our concerns about the Novartis promotional materials will lead to greater action on the part of the FDA. We see no plausible reason to delay acting to control the clearly misleading marketing materials being used by Novartis. We recognize that FDA is still working on the implementation of Guidance #213, but the promotional materials from Novartis are misleading independent of Guidance #213.

These promotional materials are linked to Guidance #213 because the type of use, including use for production purposes, that Novartis is promoting is also contrary to FDA's antibiotics policy. Since FDA's approach to addressing antimicrobial resistance is based almost entirely on adjusting labels, FDA must take steps to make sure that labels are followed and this includes not allowing drug makers to promote uses beyond what the labels allow.

KAW has identified several advertisements by Elanco that similarly make the claim that growth benefits result from preventing disease. In one, Elanco links production benefits to preventing the enteric disease ileitis in swine[4]. In the other, Elanco oddly references a study on the control of an enteric disease, necrotic enteritis, in chickens to provide evidence that production benefits result from controlling respiratory disease[5]. These products currently are approved for growth promotion but we are concerned that the linking of production claims and prevention and control

[3] http://www.pnas.org/content/109/38/15485.full
[4] http://www.elanco.us/pdfs/2011_11029_updated-tylan-tier-3-detailer_ai11164.pdf
[5] http://www.elanco.us/products-services/poultry/coccidiosis-crd-prevention.aspx

claims as done here reduces the likelihood that the implementation of Guidance #213 will lead to any public health benefits.

We ask once again that FDA require that these companies refrain from making production claims or any other unapproved claims in their marketing materials and that they refrain from making unsubstantiated claims that production benefits result from therapeutic use of medically important antibiotics.

Sincerely,

Steven Roach
Food Safety Program Director
Food Animal Concerns Trust
Keep Antibiotics Working Member Organization
3525 W. Peterson Ave., Ste 213, Chicago IL 60659
Phone 772-525-4952

CC (by email): CVM Director Dunham, CVM Deputy Director Forfa, CVM Deputy Director for Science Policy Flynn