February 8, 2024

Boehringer Ingelheim Animal Health USA Inc.
Attention: Wendi Godwin
Senior Associate Director, US Regulatory Affairs Pharmaceutical
3239 Satellite Blvd
Duluth, Georgia 30096

Re: **NADA 055-030**
Polyflex (ampicillin for injectable suspension)

CMS # 668446

Dear Ms. Godwin:

The Center of Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) has reviewed promotional communications for Polyflex (ampicillin for injectable suspension) found on the Polyflex website[1]. The website makes false or misleading claims and representations about the risks associated with use of Polyflex. Thus, the website misbrands Polyflex within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), making its distribution violative. 21 U.S.C. 352(a) and (n), 321(n), 331(a). See 21 CFR 202.1(e)(5). These violations are especially concerning from a public health perspective because the promotional communication creates a misleading impression regarding the risk of Polyflex as it relates to antimicrobial resistance and its use in human medicine.

Background

According to the Indications section of the FDA-approved package insert (PI):

> In cattle and calves, including non-ruminating (veal calves):
>
> Polyflex is indicated for respiratory tract infections: Bacterial pneumonia (shipping fever, calf pneumonia and bovine pneumonia) caused by *Aerobacter* spp., *Klebsiella* spp., *Staphylococcus* spp., *Streptococcus* spp., *Pasteurella multocida* and *E. coli* susceptible to ampicillin trihydrate.

The PI for Polyflex contains the following residue warnings information for cattle: Do not treat cattle for more than 7 days. Milk from treated cows must not be used for food during treatment, and for 48 hours (4 milkings) after the last treatment. Cattle must not be slaughtered for food during treatment, and for 144 hours (6 days) after the last treatment.

[1] Polyflex Website found at Polyflex® | Cattle Antibiotic from Boehringer Ingelheim Animal Health (bi-animalhealth.com) (last accessed 2.7.2024).

U.S. Food and Drug Administration
MPN II, Room E474
12225 Wilkins Avenue
Rockville, MD 20852
www.fda.gov

False or Misleading Risk Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading in any particular (see 21 U.S.C 352(a), (n)). The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication (21 U.S.C 321(n) and 21 CFR 202.1(e)(5))**.**

CVM found a professional sales aid titled "Polyflex detailer" (US-BOV-0512-2020-V2) on the Polyflex website, under the tab titled "Resources," as recently as December 2023. On the second page of the detailer, under the heading "Contributes to Judicious Antibiotic Use" is the following information:

> POLYFLEX is an ampicillin, while its largest competitors, Excede® (ceftiofur crystalline free acid) and Excenel® (ceftiofur hydrochloride), are both third-generation cephalosporins. Third-generation cephalosporins are used in human medicine, which causes concerns about antibiotic resistance.
>
> Choosing POLYFLEX means doing what's best for the herd, without contributing to resistance in antibiotics that are critical to human medicine.

This information is misleading because it implies that Polyflex, an aminopenicillin in the penicillin family of drugs, is not used in human medicine. According to the World Health Organization (WHO), antimicrobials used in human medicine are categorized into three classes: Critically Important, Highly Important, or Important, with critically important antimicrobials having the highest potential to impact human health.[2] Ampicillin is considered a "critically important" antimicrobial in human medicine by the WHO and is in the same class as third-generation cephalosporins, like Excede and Excenel. In addition, CVM ranks antimicrobials according to their importance in human medicine and considers ampicillin a critically important antimicrobial because it is one of limited available therapies for serious infections due to *Listeria monocytogenes* in adults and children, and Group B Streptococcus in neonates.[3]

The claims made on the detailer minimize the importance of ampicillin's use in human medicine. Stating that using Polyflex will not contribute "to resistance in antibiotics that are critical to human medicine" is false and could have dangerous consequences. Overuse or inappropriate use of ampicillin in food-producing animals could result in the emergence and selection of antimicrobial resistant foodborne bacteria which can adversely impact human health. FDA's primary concern is the potential for decreased or lost effectiveness of antimicrobial drugs in humans as a consequence of human exposure to resistant bacteria in or on food derived from treated animals. Ampicillin, as a critically important antibiotic, is a sole, or one of limited available therapies, used to treat serious bacterial infections in

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[2] World Health Organization. Critically Important Antimicrobials for Human Medicine: 6th Revision 2018

[3] Guidance for Industry #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern. Food and Drug Administration, Center of Veterinary Medicine, January 2023

people, therefore development of resistance to this antimicrobial in human medicine could have serious repercussions.

It appears that the website was recently revised, and the Polyflex detailer was replaced with a new professional sales aid titled “Polyflex Top Reasons” (US-BOV-0383-2022) which was last seen on the website on February 7, 2024. On the first page of this sales aid, under the same heading used on the previous detailer (i.e., “Contributes to Judicious Antibiotic Use”), is the following information:

> POLYFLEX is an ampicillin, while its largest competitors, Excede® (ceftiofur crystalline free acid) and Excenel® (ceftiofur hydrochloride), are both third-generation cephalosporins whose protocols must be rigid due to resistance concerns.
>
> Reach for a different family of antimicrobial with POLYFLEX to diversify antibiotic class and allow for your veterinarian to create a custom, flexible treatment plan specific to your dairy.

While this information does not minimize the importance of ampicillin’s use in human medicine, it nonetheless implies that antibiotic resistance is less of a concern when Polyflex is used instead of third-generation cephalosporins. As previously mentioned, ampicillin is considered a critically important antimicrobial in human medicine, and therefore development of resistance is a significant concern. In addition, the information presented in the detailer does not explain how using Polyflex contributes to “judicious antibiotic use.”

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Polyflex within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a) and (n), 321(n), 331(a). See 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. CVM requests that Boehringer Ingelheim cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications for Polyflex that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Polyflex.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Veterinary Medicine, Division of Pharmacovigilance and Surveillance, 12225 Wilkins Ave, MPN II Room E474, Rockville, Maryland 20852. A courtesy copy can be sent by email to CVMSurveillance@fda.hhs.gov. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter # 668446.

If you have any questions, please contact Dr. Christopher Loss by email at Christopher.loss@fda.hhs.gov.

Sincerely,

Linda A. Walter-grimm -S

Digitally signed by Linda A. Walter-grimm -S
Date: 2024.02.08 10:26:12 -05'00'

Linda Walter-Grimm, DVM
Director, Division of Pharmacovigilance and Surveillance
Office of Surveillance and Compliance
Center for Veterinary Medicine