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## The future of Stafac® (virginiamycin) for veterinary use – Company Statement

The Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) recently published two Guidances For Industry (GFI 209 and 213), which have generated considerable discussion and confusion among stakeholders in the US livestock and meat industry.

Phibro Animal Health (Phibro) has worked proactively with the CVM and in collaboration with industry to shape these GFIs and continues to work on the modernization of the Veterinary Feed Directive (VFD). Phibro's objective is to ensure that the GFIs and VFD can be implemented practically and will meet the common objectives of the various stakeholders. Phibro fully supports the responsible use of its antimicrobials used in livestock production and does not anticipate any changes in the availability of its products due to these Guidances.

Phibro is publishing this Q&A document to state our position on these important issues and to clarify some misconceptions concerning the intent and anticipated impact of these GFIs for livestock and food-producer stakeholders. Here are some frequently asked questions we have received from the industry:

**Q: What is the legal status of GFI 209 & 213? When will they become law?**

**A:** Guidance documents are written to provide direction to drug sponsors (i.e. Phibro) on option(s) the FDA would find acceptable or desirable relevant to a specific issue. They are a reflection of the FDA's current thinking on certain topics but are not legally binding. Under its own regulations, the FDA is obligated to take action if it believes a drug is unsafe. The FDA has not associated either GFI 209 or 213 with lack of safety of any of the antimicrobials currently approved.



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Every Congress for the past decade has considered one or more bills to restrict antimicrobial use in agriculture and none of these bills has gained sufficient Congressional support to become law. Phibro and industry continue to work with the CVM to find practical solutions that can be implemented without formal legislation.

**Q: What is the timing of finalizing GFI 209 & 213?**

**A:** GFI 209 was finalized on April 13, 2012. There is no date for the finalization of GFI 213 but indications are this will happen in 2013. GFI 209 and 213 are guidelines for drug sponsors. While compliance with these Guidances is voluntary, the CVM has indicated it would like to see drug sponsors making use of them within 3 years of their finalization.

**Q: What is the current status of the modernization of the VFD?**

**A:** Unlike GFI 209 & 213, the VFD is controlled by regulation and in order to be changed requires an amendment to 21 CFR §558. The CVM has indicated it hopes to have the VFD proposed rules published by the end of 2013 with implementation taking effect in 2016.

**Q: What is Phibro's position regarding GFI 209 & 213?**

**A:** Phibro supports both the overall objectives of these GFIs and the initiative to ensure veterinary oversight of the use of antimicrobials administered to livestock. We believe that livestock producers use antimicrobials at appropriate levels to ensure and maintain the health of their animals, including administration of dosages which currently may have label indications for production improvement such as "improved rate of weight gain and improved feed efficiency." Veterinarians are trained to ensure medical intervention appropriate for managing the health of animals. Early intervention with antimicrobials to prevent a disease outbreak can be highly beneficial and is a prudent course of action to ensure animal welfare.

**Q: Is *Stafac* a "Medically Important Antimicrobial" (MIA)?**

**A:** Virginiamycin, the active ingredient of *Stafac*, has never been used in human medicine; however, virginiamycin is a streptogramin antimicrobial and is in the same class of compounds as the human drug Synercid® (quinupristin/dalfopristin), which is currently classified by the CVM as a medically important antimicrobial. The antimicrobials classified as medically important are listed in the Appendix of CVM GFI-152. There is an evaluation process described in GFI-152 to determine an antimicrobial's medical importance. Synercid is currently classified as "Highly Important" (middle importance category). In 2003, when the classification was last undertaken, Synercid was regarded as a sole or limited therapy for treating vancomycin resistant *Enterococcus faecium* (VREf) infections in humans. **In 2010, the FDA determined that Synercid is not effective for VREf treatment, and removed the provisional label indication it had previously granted. Other antimicrobials have since been approved for VREf treatment.**

Phibro strongly believes that *Stafac* clearly no longer meets the FDA's criteria to be classified as "medically important". The FDA has indicated that it intends to update GFI-152 and the list of MIA's as new information becomes available. We believe that, using the current assessment criteria, *Stafac* should be reclassified with other compounds not meeting the medical importance criterion and will be removed from GFI 152. There is currently no announced date for the FDA to update GFI 152, but Phibro is pursuing this issue with the CVM.

Furthermore, the World Health Organization (WHO), which has a human health mandate, recently downgraded the medical importance rating of streptogramin antimicrobials.

**Q: What other antimicrobials used in livestock production are related to compounds on the MIA List?[1]**

**A:** There are three (3) levels of classifications in the MIA List.

The first group is the "Critically Important" category. Some commonly used antimicrobials in this category are:

- 3rd Generation Cephalosporins: (Naxcel®/Excenel®/Excede®)
- Enrofloxacin: (Baytril®)
- Macrolides: (Tylan®, Pulmotil®/Micotil®, Draxxin®, Aivlosin®)
- Sulfonamides/Diaminopyrimidines: (Rofenaid, other sulfas)

The second group is the "Highly Important" category:

- 4th Generation Cephalosporins: (Cobactan®)
- Animoglycosides: (Gentamicin, streptomycin, neomycin, etc)
- Amphenicols: (Nuflor®/Resflor®)
- Clindamycin: (Lincomycin)
- Penicillins: (Various penicillin products)
- Streptogramins: (*Stafac*)
- Tetracyclines: (Chlortetracyline, Oxytetracyline)

The third group is the "Important" category, which contains 1st & 2nd Generation Cephalosporins.

[1] All trademarks are the property of their respective owners.

**Q: What is Phibro doing in relation to the impact of GFI 209 & 213 on *Stafac*?**

**A:** Phibro has reviewed its approved virginiamycin label claims. Where usage is currently approved for production benefit (improved growth or feed efficiency), Phibro is reviewing the underlying antimicrobial mechanism of action. Administration at levels currently indicated for production benefit are commonly used to address early-stage disease prevention and typically require lower antimicrobial use rates than treatment dosages. Once a group of animals becomes clinically ill, more aggressive therapies using broad spectrum antimicrobials may be required to remediate their health than if action had been taken to prevent the disease outbreak. Phibro intends to support the lower-dose regimes by pursuing new indications for prevention and control of diseases caused by organisms susceptible to virginiamycin.

**Q: We have heard *Stafac* will be removed from the market in the future because it is classified as a Medically Important Antimicrobial (MIA). Is this true?**

**A:** No, this is false. In fact, Phibro believes the outlook for the future availability of *Stafac* has never been brighter. *Stafac* has been widely used by livestock producers in the US and other major livestock-producing countries for more than 40 years without any safety issues. *Stafac* is a narrow spectrum antimicrobial that is not absorbed from the gut and produces no measurable residues in food. In fact, the FDA conducted its own risk assessment study on *Stafac* in 2004 and found no evidence of resistance transfer from animal to human bacteria and no adverse impact on human therapy; this was confirmed by independent researchers Cox & Popken (published in the Journal of the Society for Risk Analysis, 2004).

The FDA could only remove *Stafac* or any other animal health product from the market if it was shown to be unsafe or ineffective. If either was true, the FDA would be obligated to issue withdrawal proceedings. Neither is true and no action is pending or expected with regard to *Stafac*.

**Q: As a producer, shouldn't I just stop using antimicrobials at currently approved "production" levels now to comply with the law or to get ahead of my competitors?**

**A:** All current labeled indications of *Stafac* comply with the law. Your utilization of *Stafac*, within the currently approved dose range, is in full compliance with the law and is safe and effective. Guidance documents are written to provide advice to drug sponsors. Phibro understands the CVM objectives outlined in GFI-209 and is using GFI-213 to help address the technical needs of livestock production in the long term. Phibro is committed to defending the prevention and treatment choices required by producers.

Phibro believes that maintaining the availability for use of ALL safe and effective products and their dosing options is essential for responsible animal health and welfare and to ensure sustainable meat production and a healthy food supply.

For a copy of GFI 209 & 213 please go to FDA's website at the address below:

http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf

If you have any additional questions related to the issue of streptogramin antimicrobials or any Phibro products, please feel free to contact Phibro directly at (201) 329-7374 or at Richard.Coulter@pahc.com.

Sincerely yours,

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