KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

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October 5, 2010

Dr. Margaret Hamburg
Commissioner, Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Tiamulin drug safety data and a new policy related to new drug approvals and antimicrobial resistance

Dear Commissioner Hamburg:

On behalf of Keep Antibiotics Working (KAW), we are writing to you about tiamulin, an antimicrobial drug currently approved for use in animals. Tiamulin is in the same chemical class as a human drug, retapamulin, and indirectly linked to the efficacy of another human antibiotic linezolid. The use of drugs such as tiamulin threatens the efficacy of important human drugs. Therefore, the Agency should take every opportunity to compile and keep up-to-date data on microorganisms resistant to such drugs.

FDA has opportunities to require safety data at several points in the new drug approval process, including the issuance of type 2[1] supplemental approvals (FDA, 2002). On September 8, 2010, the FDA issued a type 2 approval for a change in the concentration of tiamulin when used for disease treatment in swine. In considering the approval, the FDA had the discretion to require additional safety data, but did not act.

This was a missed opportunity. No microbial food safety data related to antimicrobial resistance has ever been evaluated by FDA on tiamulin. Moreover, in the interval since its initial approval in 1993, two important events have heightened the concern about its risk. First, in 2007, the agency approved a new *human* drug (retapamulin) in the same class (pleuromutilins) as tiamulin. Second, livestock were identified as a source of resistant *Staphylococcus aureus* infections in humans (Cuny, 2010). New evidence suggested that tiamulin use in food-producing animals could select for transferable resistance determinants that could render ineffective many important classes of drugs in treating *Staphylococcus aureus*, including pleuromutulins, oxazolidinones (linezolid) and streptogramins (Long, 2006; Miller, 2008; Kehrenberger, 2009). Potentially, the same sort of resistance-transfer may occur in the *Enterococci* (Toh, 2007; Arias, 2008).

[1] A type 2 supplemental is a change to an existing approval that could affect the safety or effectiveness of a drug, such as adding a new therapeutic claim or changing the dose or treatment regime.

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As you may be aware, linezolid is an important drug for treating serious gram positive infections including vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* (Barton, 2009; Maviglia, 2009; Moellering, 2003).

In KAW's view, the use in food-producing animals of an antimicrobial that could increase the frequency of *S. aureus* and *Enterococcal* infections resistant to a human antibiotic as critically important as linezolid should have raised red flags. The Agency should have been on the lookout for an opportunity to request up-to-date safety data.

This type 2 supplemental approval of tiamulin is the third of its kind since retapamulin was approved for humans in 2007. Each of these approvals was an opportunity for FDA to require drug sponsors to provide microbial safety data related to antimicrobial resistance. Yet in each case the Agency failed to act, apparently in conformance with its questionable policy that new safety data need not be provided unless a new approval increased the risk over existing approvals *even when the safety of existing approvals related to antimicrobial resistance has never been evaluated*.

KAW asks that FDA change its policy and evaluate the microbial safety related to antimicrobial resistance of all new approvals of medically important antimicrobial drugs including type 2 supplementals. This information is particularly important in cases where microbial safety evaluations using FDA's recommended approach, as described in Guidance for Industry #152, have never been completed. Guidance for Industry #152 was implemented by the FDA in 2003 as part of a new policy requiring drug sponsors to provide safety data related to resistance in connection with all initial new drug approval and some supplementary approvals. FDA should extend that policy to all type 2 supplementary approvals of medically important antimicrobials. Because of rapid changes in the understanding of resistance, such a policy will help ensure that FDA uses the most up-to-date science and data when making approval decisions.

In some cases, a requirement that sponsors must conduct up-to-date safety assessments could also facilitate efforts to reduce the non-therapeutic uses of antimicrobials in food-producing animals. Tiamulin, for example, is approved in swine for "increased rate of weight gain" as well as disease treatment. The more frequent provision of data by drug sponsors could guide and facilitate FDA policy related to non-therapeutic antimicrobial drug use.

FDA should adopt policies that address the seriousness of the risk to human health from antimicrobial resistance. Requiring that sponsors provide new information related to existing antimicrobial products when dose adjustments or other label changes are made is one such action that FDA can and should take.

Thank you for considering our comments.

Sincerely,

Richard R. Wood
Chair, Keep Antibiotics Working Steering Committee (KAW)

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cc: Dr. Joshua Sharfstein, Principle Deputy Commissioner, FDA
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