DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 530

[Docket No. 2006N–0106]

New Animal Drugs; Adamantane and Neuraminidase Inhibitor Anti-influenza Drugs; Extralabel Animal Drug Use; Order of Prohibition

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order prohibiting the extralabel use of anti-influenza adamantane and neuraminidase inhibitor drugs in chickens, turkeys, and ducks. We are issuing this order based on evidence that extralabel use of these anti-influenza drugs in chickens, turkeys, and ducks will likely cause an adverse event in humans.

DATES: This rule becomes effective [*insert date 90 days after date of publication in the* **Federal Register**]. Submit written or electronic comments on this document by [*insert date 60 days after date of publication in the* **Federal Register**].

ADDRESSES: You may submit comments, identified by Docket No 2006N–0106, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.

- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kim Young, Center for Veterinary Medicine (HFV–230), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 240–276–9207, e-mail: *kim.young@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

A. AMDUCA

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Public Law 103–396) was signed into law on October 22, 1994. It amended the Federal Food, Drug, and Cosmetic Act (the act) to permit licensed veterinarians to prescribe extralabel uses of approved animal and human drugs in animals. In the **Federal Register** of November 7, 1996 (61 FR 57732), we published the implementing regulations (codified at part 530 (21 CFR part 530)) for AMDUCA. The sections regarding prohibition of extralabel use of drugs in animals are found at sections 530.21, 530.25, and 530.30. These sections describe the basis for issuing an order prohibiting an extralabel drug use in animals and the procedure to be followed in issuing an order of prohibition.

We may issue a prohibition order if we find that extralabel use in animals presents a risk to the public health. Under § 530.3(e), this means that we have evidence that demonstrates that the use of the drug has caused or likely will cause an adverse event.

Section 530.25 provides for a public comment period of not less than 60 days. It also provides that the order of prohibition will become effective 90 days after the date of publication, unless we revoke the order, modify it, or extend the period of public comment. The list of drugs prohibited from extralabel use is found in § 530.41.

B. Adamantane and Neuraminidase Inhibitor Anti-influenza Drugs

An influenza type A pandemic is a global outbreak of disease that occurs when a new influenza A virus subtype appears or ‘‘emerges’’ in the human population, causes serious illness in people, and then spreads easily from person to person worldwide (Ref. 1). Pandemics are different from seasonal outbreaks or ‘‘epidemics’’ of influenza. Seasonal outbreaks are caused by subtypes of influenza viruses that already circulate among people. In contrast, pandemics are caused by new subtypes, by subtypes that have never circulated among people, or by subtypes that have not circulated among people for a long time (Ref. 1). Historically, many influenza epidemics in people have originated in birds. The human influenza pandemic of 1918 is thought to have developed in birds (Ref. 2) and the current pandemic threat is coming from an avian influenza outbreak that started by affecting poultry flocks in Southeast Asia (Ref. 3) with subsequent outbreaks detected on other continents (Ref. 4). The influenza A (H5N1 subtype) causing the outbreak in Asia has already demonstrated the ability to transmit zoonotically from birds to people (Ref. 3). Many experts believe the H5N1 subtype of the influenza A virus will eventually be capable of spreading easily from person to person, creating a new pandemic (Ref. 5).

The first line of defense for any influenza outbreak in people is vaccination (Ref. 6). Influenza vaccines are among the most important interventions in an influenza epidemic, but are expected to have their optimal effect only if the vaccine is adequately matched to the circulating viral strain. Confronted with a fast moving influenza pandemic, there may not be enough time to characterize the virus, develop a vaccine, distribute it widely, and administer it to enough people to make a difference (Ref. 1). If this situation occurs in

the United States, we will become heavily dependent upon our second line of defense, which is the administration of anti-influenza drugs. There are currently four approved antiviral drugs, in two classes, for the treatment or prevention of influenza A in humans. These are the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir) (Ref. 7). They are not approved for use in the treatment or prevention of influenza in animals.

Anti-influenza drugs are intended to be administered when appropriate to people that are clinically ill with influenza to reduce the time to improvement of influenza symptoms. In addition, they may be administered to people exposed to influenza, to prevent clinical illness. Although these drugs are not a substitute for vaccination, in selected circumstances they have also been included in outbreak control strategies. To limit the impact of a pandemic influenza outbreak it will be critical that effective antiviral therapies be available for treatment and prophylaxis of disease in humans. For this reason the World Health Organization (WHO) considers these drugs critically important antimicrobials for humans (Ref. 8).

FDA is concerned regarding the ease with which influenza A viruses can become drug-resistant as a result of selective pressure induced by the use of anti-influenza drugs. FDA is also concerned that the extralabel use of these drugs in animals is likely to lead to the emergence of resistant strains of influenza A, particularly when such extralabel use could involve administration to large numbers of animals. If these drug-resistant strains infect humans, it is likely that the approved anti-influenza drugs will no longer be effective for treating or preventing disease in those people. Therefore, FDA is issuing an order prohibiting the extralabel use of adamantane and

neuraminidase inhibitor anti-influenza drugs in chickens, turkeys, and ducks because, as discussed in sections II and III of this document, the agency has determined that such extralabel use likely will cause an adverse event and as such presents a risk to the public health. FDA may expand the list of animal species affected as new data becomes available.

II. Adamantanes

The adamantanes are the older of the two classes of anti-influenza drugs, the oldest drug having been on the market for over 30 years. Adamantane-resistant influenza viruses have been observed to emerge readily after exposure to these drugs in both humans and animals (Ref. 9). Moreover, such viruses can be transmitted from human to human without any loss of pathogenicity (Refs. 9 and 10). Chicken flocks in China and other parts of Asia have reportedly been treated with amantadine starting in the late 1990's (Refs. 8, 11, and 12). Amantadine resistance among H5 avian influenza viruses was 0 percent in both North America and Southeast Asia before this time. Between 2000 and 2004, amantadine resistance in H5 avian influenza viruses in Southeast Asian flocks rose to 31 percent while remaining at 0 percent in North America (Ref. 12). Although the H5N1 subtype of influenza A has not yet been found in the United States, some reports indicate that since 2003, many human and most avian isolates tested in other countries are now resistant to amantadine and rimantadine (Refs. 9 and 10).

Genetic studies have shown that the resistance of influenza A viruses (isolated from both birds and people) to amantadine and rimantadine, including resistance in the H5N1 subtype, is associated with an amino acid substitution in the M2 protein (Refs. 9 and 10). More specifically, genetic studies have shown that adamantane-resistant H5N1 virus isolated from both

birds and people in Southeast Asia has an amino acid substitution at position 31 of the M2 protein (Ref. 9). This suggests that when the H5N1 influenza virus moved from birds to people it carried with it the amino acid substitution resulting in adamantane resistance in humans.

Birds are regarded as the main reservoir and source of influenza A viruses for mammals, including humans (Ref. 13). Chickens, ducks, turkeys, guinea fowl, quail, pheasants, and other birds are susceptible, but disease outbreaks most frequently occur in chickens and turkeys (Ref. 14). Avian influenza viruses are categorized as to their ability to cause disease in chickens and are referred to as having either low or high pathogenicity. High pathogenicity avian influenza viruses identified more recently in Asia have exhibited increased virulence for chickens with some strains causing severe disease in ducks (Ref. 15). Reports indicate that H5N1 isolates from Asia replicate and transmit efficiently in ducks and can cause effects that range from complete absence of clinical disease to severe disease and death (Ref. 16).

In the United States, chickens, turkeys, and ducks are raised commercially in large numbers and in close confinement. Based on surveys conducted by the U.S. Department of Agriculture, the total inventory of live chickens and turkeys present on U.S. farms at any given time is approximately 2 billion and 93 million birds, respectively (Ref. 17). In 2005, there were an estimated 9 billion chickens, 248 million turkeys, and 28 million ducks slaughtered in the United States (Ref. 18). Each time an influenza A virus is exposed to an anti-viral drug within an individual infected animal or human there is a chance that a drug resistant virus will emerge. The greater the number of infected individuals exposed to anti-viral drugs the greater the number of opportunities for resistance to emerge. The large number of birds that could potentially be

treated at a given time within a typical poultry production facility would result in a large number of individual animals exposed to anti-viral drug thereby substantially increasing the chances of selection for drug-resistant viral mutants. In addition, mass medication of birds (e.g., via drinking water) is likely to result in inconsistencies in dosing levels contributing further to the emergence of resistance. Furthermore, close confinement would likely accelerate the spread of drug-resistant viruses between birds.

Due to evidence indicating that the use of adamantanes in chicken flocks in Asia likely contributed to resistance emergence, FDA believes that the use of these drugs in U.S. chicken flocks would likely result in resistance emergence here as well. In addition, since turkeys and ducks are also susceptible to avian influenza and are often raised under similar husbandry conditions as chickens, FDA believes that the use of adamantanes in turkeys and ducks would also likely result in resistance emergence. Furthermore, the recent cases in Southeast Asia demonstrate that zoonotic subtypes of influenza A, such as H5N1 that have become resistant to the adamantanes, are still capable of transmission to humans. Therefore, FDA has concluded that the extralabel use of the adamantane class of drugs in chickens, turkeys, and ducks will likely cause an adverse event and thus presents a risk to the public health.

III. Neuraminidase Inhibitors

The neuraminidase inhibitor drugs (oseltamivir and zanamivir) are a newer class of drugs, first approved for treatment of influenza in humans in 1999. Although neuraminidase inhibitors appear to be associated with a lower frequency of resistance emergence than the adamantanes (Ref. 19), emergence of influenza A resistance to oseltamivir during treatment has been documented in humans. For example, oseltamivir-resistant viral strains have been detected

in up to 16 percent of children with human influenza A (H1N1) who have received oseltamivir (Ref. 20) and recent reports from Viet Nam describe two human patients who contracted avian influenza A (H5N1) and subsequently died of the infection while receiving oseltamivir therapy (Ref. 21). Oseltamivir-resistant strains were isolated from both of these patients (Ref. 21). Although data are limited regarding clinical emergence of resistance to zanamivir (which has been used much less in humans than oseltamivir), mutant virus with reduced susceptibility to zanamivir was occasionally observed to emerge in immunocompromised patients infected with influenza virus after treatment with zanamivir or oseltamivir (Ref. 22). In addition, *in vitro* studies have shown that exposure of influenza viruses to increasing concentrations of zanamivir have resulted in viral mutations conferring reduced susceptibility to the drug (Ref. 23). Furthermore, cross-resistance—where resistance to one drug means the virus would be resistant to the other—has been observed between zanamivir-resistant and oseltamivir-resistant influenza virus mutants generated *in vitro* (Refs. 23, 24, and 25). Based on this information, FDA believes that extralabel use of either neuraminidase inhibitor drug (oseltamivir or zanamivir) is likely to increase the risk of emergence and spread of drug-resistant influenza virus.

As seen with the adamantane class of drugs, concerns have been raised that use of the neuraminidase inhibitors in poultry will similarly lead to the emergence of influenza A virus that is more resistant to neuraminidase inhibitors (Ref. 8). FDA is not aware of studies that have investigated whether the use of these drugs in poultry is associated with the emergence of influenza A virus that is resistant to neuraminidase inhibitors. However, FDA believes the reports of resistance cited previously combined with the evidence of

resistance to the adamantane class reported in both poultry and humans indicate that resistance to the neuraminidase inhibitor drugs is likely to emerge with their use in poultry.

While some reports indicate that mutations conferring resistance to the neuraminidase inhibitors have generally been associated with reduced viral fitness and transmissibility (Refs. 19 and 26), studies have found that some oseltamivir-resistant influenza A strains were transmissible among ferrets (Refs. 26 and 27). Therefore, although the data regarding neuraminidase-inhibitor-resistant influenza A are limited, FDA believes this data combined with data on the transmissibility of adamantane-resistant influenza A are adequate to conclude that if zoonotic influenza A were to emerge in U.S. poultry and became resistant to the neuraminidase-inhibitors, it is likely that such virus would be transmissible to humans.

The ''adverse event'' associated with extralabel use of neuraminidase inhibitor anti-influenza drugs in chickens, turkeys, and ducks is therefore the same as that discussed earlier with regard to extralabel use of adamantanes. The agency's basis for prohibiting extralabel uses in chickens, turkeys, and ducks of neuraminidase inhibitor anti-influenza drugs is also the same as that for adamantanes. That is, the extralabel use of neuraminidase inhibitor anti-influenza drugs in chickens, turkeys, and ducks likely will contribute to the emergence of drug resistance in the influenza A virus and compromise human therapy. Furthermore, given that some reports indicate that many of the human and avian influenza A (H5N1) isolates tested since 2003 have been reported to be resistant to the adamantane drugs (Refs. 9 and 10), and because H5N1 may occur in the Unites States, it is particularly important that steps be taken to preserve the effectiveness of the neuraminidase inhibitor class of drugs.

Therefore, the agency is acting in the interest of the public health and prohibiting the extralabel use of neuraminidase inhibitor anti-influenza drugs in chickens, turkeys, and ducks.

IV. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

V. Order of Prohibition

Therefore, I hereby issue the following order under §§ 530.21 and 530.25. We find that extralabel use of anti-influenza A drugs of the adamantane and neuraminidase inhibitor classes of drugs in chickens, turkeys, and ducks likely will cause an adverse event which constitutes a finding that extralabel use of these drugs presents a risk to the public health. Therefore, we are prohibiting the extralabel use of anti-influenza drugs of the adamantane and neuraminidase inhibitor classes of drugs in chickens, turkeys, and ducks.

VI. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**). You may view them between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. CDC Web site: *http://www.cdc.gov/flu/pandemic/keyfacts.htm*, March 2, 2006.

2. Taubenberger, J.K., et al., ''Characterization of the 1918 Influenza Virus Polymerase Genes,'' *Nature*, vol. 437, pp. 889–893, 2005.

3. WHO Web site: *http://www.who.int/csr/disease/avian__influenza/avian__faqs/en/index.html#whatis*, March 2, 2006.

4. OIE Update on Avian Influenza in Animals (Type H5); 20 February, 2006: *http://www.oie.int/downld/AVIAN%20INFLUENZA/A__AI-Asia.htm*, March 2, 2006.

5. Pan American Health Organization Strategic and Operational Plan for Responding to Pandemic Influenza (draft), September 23, 2005.

6. CDC Morbidity and Mortality Weekly Report, vol. 54, RR–8, 2005.

7. FDA/CDER Web site: *http://www.fda.gov/cder/drug/antivirals/influenza/default.htm*, March 2, 2006.

8. Joint FAO/OIE/WHO statement: ''Use of Antiviral Drugs in Poultry, a Threat to Their Effectiveness for The Treatment of Human Avian Influenza,'' November 11, 2005, WHO web site: *http://www.who.int/foodsafety/micro/avian__antiviral/en/index.html*, March 2, 2006.

9. Bright, R.A., et al., ''Incidence of Adamantane Resistance Among Influenza A (H3N2) Viruses Isolated Worldwide From 1994 to 2005: A Cause For Concern,'' *Lancet*, vol. 366, pp. 1175–1181, 2005.

10. Wong, S.S.Y., et al., ''Avian Influenza Virus Infections in Humans,'' *Chest*, vol. 129, pp. 156–168, 2006.

11. Cyranoski, D., ''China's Chicken Farmers Under Fire For Antiviral Abuse,'' *Nature*, vol. 435, pp. 1009, 2005.

12. Ilyushina, N.A., et al., ''Detection of Amantadine-Resistant Variants Among Avian Influenza Viruses Isolated in North America and Asia,'' *Journal of Virology*, vol. 341, pp. 102–106, 2005.

13. Webster, R.G., ''The Importance of Animal Influenza for Human Disease,'' *Vaccine*, vol. 20, pp. S16–S20, 2002.

14. FAO Animal Health Special Report: *http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/avian.html*, March 2, 2006.

15. Swayne, D.E., ''Occupational and Consumer Risks From Avian Influenza Viruses,'' Developments in Biologicals, vol. 124, pp. 85–90, 2006.

16. Sturm-Ramirez, K.M., et al., ''Are Ducks Contributing to the Endemicity of Highly Pathogenic H5N1 Influenza Virus in Asia?,'' *Journal of Virology*, vol. 79, pp. 11269–11279, 2005.

17. USDA / National Agricultural Statistics Service, 2002 Census of Agriculture.

18. USDA / National Agricultural Statistics Service, January 31, 2006 report.

19. Institute of Medicine of the National Academies, Knobler, S.L., et al., editors, Workshop summary: ''The Threat of Pandemic Influenza. Are We Ready?'' 2005. *http://www.nap.edu/books/0309095042/html*, March 2, 2006.

20. WHO Writing Committee, ''Avian Influenza A (H5N1) Infection in Humans,'' *The New England Journal of Medicine*, vol. 353, pp. 1374–1385, 2005.

21. de Jong, M.D., et al., ''Oseltamivir Resistance During Treatment of Influenza A (H5N1) Infection,'' *The New England Journal of Medicine*, vol. 353, pp. 2667–2672, 2005.

22. Ison, M.G., ''Recovery of Drug-Resistant Influenza Virus from Immunocompromised Patients: A Case Series,'' *Journal of Infectious Diseases*, vol. 193, pp. 760–764, 2006.

23. U.S. Prescribing Information for Tamiflu (Roche Pharmaceuticals, December 2005) and Relenza (GlaxoSmithKline, April 2003).

24. Jackson, D., et al., ''Characterization of Recombinant Influenza B Viruses With Key Neuraminidase Inhibitor Resistance Mutations,'' *Journal of Antimicrobial Chemotherapy*, vol. 55, pp. 162–169, 2005.

25. Mishin, V. P., ''Susceptibilities of Antiviral-Resistant Influenza Viruses to Novel Neuraminidase Inhibitors,'' *Antimicrobial Agents and Chemotherapy*, vol. 49, pp. 4515–4520, 2005.

26. Moscona, A., ''Neuraminidase Inhibitors for Influenza,'' *The New England Journal of Medicine*, vol. 353, pp. 1363–1373, 2005.

27. Moscona, A., ''Oseltamivir Resistance—Disabling Our Influenza Defenses,'' *The New England Journal of Medicine*, vol. 353, pp. 2633–2636, 2005.

List of Subjects in 21 CFR Part 530

Administrative practice and procedure, Advertising, Animal drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director of the Center for Veterinary Medicine, 21 CFR part 530 is amended as follows:

PART 530—EXTRALABEL DRUG USE IN ANIMALS

■ 1. The authority citation for 21 CFR part 530 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b, 371, 379e.

■ 2. In § 530.41, add and reserve paragraph (c) and add paragraph (d) to read as follows:

§ 530.41 Drugs prohibited for extralabel use in animals.

* * * * *

(c) [Reserved]

(d) The following drugs, or classes of drugs, that are approved for treating or preventing influenza A, are prohibited from extralabel use in chickens, turkeys, and ducks:

(1) Adamantanes.

(2) Neuraminidase inhibitors.

Dated: March 14, 2006.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

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