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Food and Drug Administration  
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The Center for Science in the Public Interest (“CSPI”) appreciates the opportunity to comment on the proposed rule establishing a process for setting tolerances for residues of unapproved new animal drugs in imported food [Docket No. FDA-2001-N-0075; 77 Fed. Reg. 3653, Jan. 25, 2012]. CSPI is a non-profit consumer advocacy and education organization that focuses largely on food safety and nutrition issues. It is supported principally by the 850,000 subscribers to its Nutrition Action Healthletter and by foundation grants.

CSPI opposes this ill-advised rule because of the serious repercussions it will have to public health, consumer confidence, and the domestic drug approval process. The rule fails to provide for adequate review of an unapproved new animal drug application, and is missing necessary assurances that the use of an unapproved new animal drug is necessary, efficacious, appropriate and limited to its intended purpose. Furthermore, we believe the Food and Drug Administration (“FDA”) has failed to account for all of the costs and has demonstrated no substantial benefits of the proposed rule to consumers. We urge FDA to withdraw the rule until it can be revised along the lines recommended below.

The proposed rule compounds the risks consumers face from unapproved animal drugs. It would permit FDA to set tolerances for residues of unapproved new animal drugs in imported food. Those same residues found in food from an animal raised in the United States would be evidence of unsafe use under 21 U.S.C. § 360b and cause the food to be adulterated under 21 U.S.C. § 342(a)(1)(C)(ii). It makes little sense to extend a privilege to foreign food producers that would result in prosecution were they to engage in the same practice domestically. CSPI recognizes that Congress granted FDA authority to establish tolerances in the Animal Drug Availability Act of 1996. But, we question why the nation’s premier public health agency should elect to exercise so misguided a grant of discretionary authority 16 years later by proposing a rule that results in such an absurd outcome.

1. Proposed rule increases risks to public health and will undermine consumer confidence in the safety of imported food.

Imported food makes up a substantial portion of the American diet. Approximately 15 percent of the food Americans consume is produced somewhere else with 80 percent of seafood, 61 percent of honey, 10 percent of red meat, 3 percent of dairy products consumed in the U.S.
being imported. Each of these commodities has a known risk of containing drug residues that may result in allergic reactions or other serious side effects or whose conversion products can cause serious health consequences. The substantial proportion of imported food derived from animals identifies animal drug residues in imported food as an area of considerable risk to consumers.

Consumers are already at a high risk of exposure to unapproved animal drugs in imported food because of FDA’s poor record of border inspections. FDA tests little of the food imported into this country for drug residues presently. For example, FDA samples only 2 percent of imported seafood for veterinary drug residues. This low sampling rate compares unfavorably to that of our principle trading partners, the European Union (50%), Japan (18%) and Canada (15%). Forty-three percent of the inspections in the U.S. turn up violations, suggesting a substantial amount of chemically contaminated seafood may reach consumers annually. When CSPI reviewed FDA’s import refusals, we found unsafe drug residues were the fourth most common reason cited for rejecting imported seafood at the border. The problem of unapproved animal drug residues in imported food is by no means limited to seafood. For example, chloramphenicol, fluoroquinolone and sulfonamide residues have turned up in honey imported from China.

FDA establishes residue tolerances, but it is the Food Safety and Inspection Service (“FSIS”) that uses them to test the safety of domestically produced and imported meat, poultry and egg products. The absence of any indication that FDA coordinated the proposed rule with FSIS along with that agency’s low rate of sampling for drug residues is cause for consumer concern. FSIS physically examines as little as 10 percent of the 3.4 billion pounds of imported food under its jurisdiction and samples only a portion of that percentage for drug residues. Establishing tolerances for unapproved new animal drugs may require FSIS to further subdivide a limited sampling program to test that residues of the unapproved drugs are within the tolerance.

The proposed rule does not explain how FDA will assess an acceptable daily intake (“ADI”). This may differ for U.S. consumers as compared to consumers in a country where an unapproved new animal drug is in use because of differing national dietary preferences. For example, Americans consume more beef per capita than any other country except Argentina and Uruguay. This is problematic for consumers. Under the proposed rule, the applicant is required

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3 Id. at 7234.
4 Id.
7 Id.; GAO, Food Safety: Agencies Need to Address Gaps in Enforcement and Collaboration to Enhance Safety of Imported Food, GAO-09-873, 50 (Oct. 14, 2009) (FSIS re-inspects 100 percent of imports, but most of these are “skipped shipments” meaning the inspection only looks at the general condition and labeling of the shipment. In 2008, FSIS did a more intensive physical examination of only 9.4 percent of imports.)
to submit a proposed tolerance and supporting human food safety information.\(^9\) If the applicant sets an invalid ADI – i.e. relying on consumption studies in the country where the drug is approved – that may result in higher exposures than are safe in the U.S. population.

Consumers already express little trust in the safety of imported food. Internal polling of CSPI members found that 79 percent were very concerned over the safety of imported food compared to 52 percent who expressed the same level of concern for the safety of domestic food.\(^10\) This level of distrust appears in public polling as well. Consumers Union reported that 81 percent of consumers it polled expressed concern over the safety of imported food.\(^11\) Meanwhile, the International Food Information Council found that 61 percent of Americans believe that imported food is less safe than domestic food, with 50 percent citing less regulation as the top reason.\(^12\) Consumer confidence is likely to be shaken further by realization that unapproved animal drug residues may be present in imported food, even though FDA declares them safe.

Consumers recall the horror of thalidomide which was approved in Europe, but kept out of the U.S. market by FDA. Consumers will be concerned that the safeguard of careful FDA review which protected them in that case will be absent under this proposed rule. In addition to eroding trust in FDA oversight, severe economic damage may be done to food marketers by this proposed rule. The recent incident involving the antifungal carbendazim in orange juice is an example. Although it was present in levels which FDA said were safe, sales of orange juice fell at rates of from 12 to 16 percent, a far faster decline than price changes alone could account for.\(^13\) It is reasonable to assume that consumers will react the same way as they learn imported food contains residues from unapproved animal drugs.

2. Process for requesting an import tolerance undermines the drug approval program and endangers consumers.

The animal drug approval process in the U.S. protects the American public from dangerous and ineffective medicines and from unscrupulous manufacturers. With regard to food animals, it serves the further purpose of ensuring any residue (or its byproducts) remaining in food is not harmful to human health. In the 73 years since passage of the Federal Food, Drug, and Cosmetic Act of 1938, consumers have relied on FDA to review and approve applications for new animal drugs that are effective and safe for their intended use.

In contrast, the proposed rule replaces FDA’s drug approval process with an abbreviated review to set a tolerance for any unapproved new animal drug provided it is lawfully used in another country.\(^14\) That the tolerance review process is at best cursory is evident from the time FDA intends to spend reviewing an application. FDA estimates each review for a tolerance will

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9 § 510.205(b)(4)(iii) & (iv).
13 Kevin Bouffard, Fewer Orange Juice Shipments Tainted by Carbendazim, The (Lakeland, Fla.) Ledger, April 5, 2012.
14 § 510.201.
require 100 hours of a mid-level FDA employee’s time.\(^\text{15}\) This compares to 6 months to a year for review and approval of a new animal drug by a team of CVM personnel, including veterinarians, animal scientists, biostatisticians, chemists, microbiologists, pharmacologists and toxicologists.\(^\text{16}\)

FDA will not be able to guarantee the tolerance results from appropriate use of an unapproved new animal drug. The proposed rule only requires that a tolerance be either the maximum residue limit in the Codex Alimentarius, if one exists, or one proposed by the applicant.\(^\text{17}\) Missing from the proposed rule is –

- Any requirement for the country in which the unapproved new animal drug is legally used to have an equivalent animal drug regulatory program;
- A requirement for the applicant to submit the record of the foreign country’s approval actions and the approved uses of the new animal drug; and,
- A requirement for food containing a new animal drug residue to originate in a country that has approved and is actively monitoring the drug’s use.

These missing elements mean that FDA will be unable to assure the public that an approval came from, and is monitored by, an equivalent drug regulatory program, that the approval process decision was based on the best available science, and that the residues are the result of legal use in the country the food originates from.

The proposed rule will have other unintended consequences caused by the reduced incentives for manufacturers to seek FDA approval for new animal drugs. Not only would the tolerance evaluation save time between application and approval, it also avoids the fees associated with new drug approvals. CSPI anticipates most manufacturers who request a tolerance will do so if the new animal drug does not have a substantial market in the U.S. or the drug is unlikely to survive a stringent drug approval review process. If that proves correct, then FDA has underestimated the demand for tolerances, and has failed to account fully for review costs and lost revenues it will suffer.

In addition to the added burden and reduced fee collections if requests for tolerances become more common, FDA will be unable to assure the public that unapproved new animal drugs met standards for purity and effectiveness or were used effectively or appropriately. This is another consequence of the proposed rule’s failure to require FDA to consider the equivalence of the foreign country’s drug regulatory program. FDA’s lack of authority to inspect foreign


\(^{16}\) 21 U.S.C. § 512(c) requires FDA to issue a decision on a new animal drug application within 180 days (6 months). FDA reported in 2011 that it met that requirement 90 percent of the time. FDA, *FY2011 ADUFA Performance Report to Congress*. The Center For Veterinary Medicine describes the approval process thus: “A team of CVM personnel, including veterinarians, animal scientists, biostatisticians, chemists, microbiologists, pharmacologists, and toxicologists, reviews the NADA. If the CVM team agrees with the sponsor’s conclusion that the drug is safe and effective if it is used according to the proposed label, the NADA is approved and the drug sponsor can legally sell the drug.” FDA, *From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process*, at http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm (last accessed Apr. 19, 2012).

\(^{17}\) § 510.205(b)(5)(iv)(A) & (B).
drug manufacturers that don’t produce for the U.S. market and lack of access to information on foreign on-farm uses further complicate the agency’s ability to ensure residues result from legal uses of an unapproved new animal drug. As a result, the proposed rule is likely to expose consumers to potential hazards from unapproved animal drugs that are not or could not be approved for use in this country, but turn up, nonetheless, as residues in the food they eat.

3. Recommendations.

CSPI recommends that FDA withdraw the rule until it is revised to ensure imported food meets the same standards for safety as domestically produced food. As proposed, the rule will expose consumers to potentially unsafe new animal drugs and their by-products. While CSPI opposes a process that will allow unapproved animal drug residues to enter the food supply, we recognize that this proposed rule is merely giving substance to a poorly considered and misguided statutory provision. However, FDA should not compound bad law with bad rules. The discussion above identifies a number of weaknesses in the proposed rule. To address these and other flaws within the rule as proposed, CSPI recommends the following changes:

A. When applications for a tolerance are allowed.

- Information supplied to FDA in support of a tolerance should use an ADI based on U.S. consumption patterns.
- Tolerances should only be considered for an unapproved new animal drug that is used solely for therapeutic purposes. This is consistent with Congressional intent that a tolerance would apply in situations where the drug is for treating diseases and conditions that do not occur in the U.S.\(^{18}\)
- Tolerances should not be considered if an FDA approved animal drug addresses the condition for which the unapproved new animal drug is indicated.
- Tolerances should only be considered for unapproved new animal drugs manufactured and used in a country that FDA has determined has an equivalent (or comparable) food safety system and drug approval regulatory program.

B. Conditions of use.

- Approved tolerances should only apply to food originating from the country where the unapproved new animal drug is in legal use.
- FDA should have the right to limit the uses of a drug for which a residue is allowed, and require an exporting country to certify that the unapproved new animal drug was only used for an FDA approved purpose.

C. Importer responsibilities.

- Importers should be required to notify FDA or FSIS that they are importing products under an applicable tolerance. This will provide the agencies with an opportunity to target inspections for determining that the food is within the tolerance. It will also allow

FDA and FSIS to discriminate between legal and illegal use of an unapproved new animal drug when residues are found during random testing.

- Importers should be required to obtain documentation showing that residues are the result of legal use of an unapproved new animal drug in the country where the food originates.

**D. Definition of “safe” and provisions for notice.**

- The proposed rule should define “safe” as meaning the level of risk an applicant must establish for an unapproved new animal drug residue is zero.
- Imported food that is likely to contain an unapproved new drug residue should be labeled as “May contain residues of animal drugs that are not approved for use in the United States.”
- The rule should specify that a drug manufacturer of an unapproved new animal drug for which a tolerance is established must comply with requirements to report adverse drug events.
- FDA should require drug manufacturers to notify the agency of any change in the status of an approved drug (including any adverse events) in any country where it is in use.

**E. Additional changes.**

- § 510.205(b) should include a requirement for the applicant to submit information on alternative treatments or competing animal drugs and explain why the use of an unapproved new animal drug is necessary in light of alternatives.
- § 510.205(b) should be further revised to require an applicant to submit an affidavit that there are no FDA approved animal drugs to treat the disease of condition for which the unapproved new animal drug is indicated.
- § 510.207(a)(1) should clarify that the evidentiary standard for seeking a revocation is evidence to show a reasonable basis from which serious questions may be inferred about the ultimate safety of the unapproved new animal drug residue and any substance that may be formed as a result of the unapproved new animal drug’s use.\(^\text{19}\) As proposed, the rule appears to require consumers to bring conclusive evidence in order to obtain a review.

CSPI is also concerned that FDA has not accounted for all the costs associated with the proposed rule. It is also disconcerting that FDA could not identify a single benefit accruing to consumers in its cost-benefit analysis. We therefore recommend that FDA revise its analysis to factor in the following:

- FDA should describe and quantify the benefits consumers will experience. Currently, the benefit analysis fails to identify any benefit to consumers from allowing tolerances for unapproved new animal drugs.
- The cost analysis should account for economic effects that can reasonably be anticipated:
  - FDA should account for costs consumers and manufacturers of competing animal drugs will incur in responding to requests for a tolerance.

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\(^{19}\) This the standard announced in Docket No. 00N-1571, at 5, Mar. 16, 2004.
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- FDA should consider how a loss of consumer confidence in the safety of imported food may affect the import market once the public is aware that unapproved animal drug residues and their by-products are in their food supply.
- FDA should include the cost of lost markets to manufacturers of approved animal drugs due to foreign producers substituting unapproved new animal drugs for which FDA has established a tolerance.
- FDA does not estimate costs that may be incurred by it and FSIS if the “practicable method for determining the quantity” of an unapproved new animal drug requires additional tests to be added to import sampling and testing programs.
- Since some drug manufacturers may elect to seek a tolerance in lieu of full approval, FDA should include lost revenues in its calculation of the cost to the government.

4. Conclusion.

CSPI believes there is no reasonable argument for exposing consumers to the risk posed by imported food contaminated with residues from unapproved new animal drugs. We know that lax standards and weak enforcement in other countries already exposes consumers to dangerous drug residues in imported food. The one situation cited by Congress of when a tolerance might be necessary is unconvincing. Manufacturers of drugs that treat animal diseases or conditions that only occur in other countries should seek full FDA approval of such drugs if the intended use is for treating animals destined for the U.S. market. It is absurd to permit residues in imported food that if used in the U.S. would cause domestically produced food to be adulterated and unmarketable.

Not only does the proposed rule produce situations that are unfair to domestic producers and responsible drug manufacturers, it also risks public health and results in unintended consequences such as shaking public confidence in FDA’s ability to oversee the safety of the food supply. However, if FDA is intent on using its authority to establish residues for unapproved new animal drugs in imported food, then it should at a minimum ensure the rule is as protective of consumer health and safety as possible. As drafted, that is not the case, and the proposed rule should be withdrawn for further revision.

Respectfully submitted,

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