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Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271

[Docket No. 2005N–0373]

RIN 0910–AF54

Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to prohibit the use of certain cattle material in, or in the manufacture (including processing) of, drugs, biologics, and medical devices intended for use in humans and human cells, tissues, and cellular and tissue-based products (HCT/Ps) (collectively, medical products for humans), and in drugs intended for use in ruminant animals (drugs for ruminants). FDA is also proposing new recordkeeping requirements for medical products for humans and drugs for ruminants that are manufactured from or otherwise contain material from cattle. FDA is proposing these actions as part of its continuing efforts to strengthen defenses against the potential risk of exposure to, and spread of, bovine spongiform encephalopathy (BSE) and related human disease in the United States.

DATES: Submit written or electronic comments on the proposed rule by March 13, 2007. Submit written comments on the information collection requirements by February 12, 2007. Requests for an informal hearing on the proposed ban related to medical devices must be submitted by February 12, 2007.

ADDRESSES: You may submit comments, identified by Docket No. 2005N–0373 and RIN number 0910–AF54, 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 detailed instructions on submitting comments and additional information on the rulemaking process, see section VII ''Effective Date and Opportunity for Public Comment'' in 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.

Information Collection Provisions: To ensure that comments on the information collection are received, Office of Management and Budget (OMB) recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT:

For information concerning products regulated by the Center for Drug Evaluation and Research: Vikki Kinsey, Center for Drug Evaluation and Research (HFD–006), Food and Drug Administration, 5515 Security Lane, rm. 5110, Rockville, MD 20852, 301–443–5578, e-mail: *vikki.kinsey@fda.hhs.gov*.

For information concerning products regulated by the Center for Biologics Evaluation and Research: Stephen M. Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, rm 594N, Rockville, MD 20852–1448, 301–827–6210, e-mail: *stephen.ripley@fda.hhs.gov*.

For information concerning products regulated by the Center for Devices and Radiological Health: Scott G. McNamee, Center for Devices and Radiological Health, Food and Drug Administration, 2094 Gaither Rd., rm. 230, Rockville, MD 20850, 240–276–0105, e-mail: *scott.mcnamee@fda.hhs.gov*.

For information concerning products regulated by the Center for Veterinary Medicine: Michael J. Popek, Center for Veterinary Medicine (HFV–144), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6462, e-mail: *michael.popek@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

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I. Introduction

On January 26, 2004, the U.S. Department of Health and Human Services announced its plan to establish new safeguards to strengthen existing firewalls against transmission of BSE in the United States. Consumption of products contaminated with the agent that causes BSE has been linked to the human disease variant Creutzfeldt-Jakob disease (vCJD). Current protections against the spread of BSE in the United States include:

- FDA's ruminant feed regulation (the 1997 ruminant feed rule) (62 FR 30936, June 5, 1997) (see section V.A.8 of this document for definition of ruminant),
- U.S. Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS) interim final rule banning specified risk materials (SRMs) and certain other cattle material in human food (the USDA/FSIS IFR) (69 FR 1862, January 12, 2004; as amended, 70 FR 53043, September 7, 2005),
- FDA's interim final rule banning the use of SRMs and certain other cattle material in human food, including dietary supplements, and cosmetics (the Foods IFR) (69 FR 42256, July 14, 2004; as amended, 70 FR 53063, September 7, 2005), and
- Import controls.

FDA also has requirements for establishment and maintenance of records concerning use of materials derived from cattle in human food and cosmetics (the Foods Recordkeeping/Access final rule) (71 FR 59653, October 11, 2006). In addition, FDA, in conjunction with USDA, issued an advance notice of proposed rulemaking (ANPRM) to solicit comment on additional measures under consideration, including measures related to animal feeds (the joint ANPRM) (69 FR 42288, July 14, 2004). On October 6, 2005 (70 FR 58570), we issued a proposed rule that would prohibit certain cattle materials from all animal feed (FDA 2005 Animal Feed proposed rule).

In this medical products proposed rule, FDA is proposing to prohibit use of SRMs and certain other cattle material in, or in the manufacture (including processing) of, medical products for humans and drugs for ruminants because of the risk of transmission of BSE. FDA is also proposing recordkeeping requirements for medical products for humans and drugs for ruminants that are manufactured from or otherwise contain material from cattle to ensure compliance with the prohibitions in this proposed rule. The proposed requirements are consistent with the requirements in the USDA/FSIS IFR and the Foods IFR, as well as those in the Foods Recordkeeping/Access final rule. The proposed requirements in this medical products proposed rule only apply to medical products for humans and drugs for ruminants. They do not apply to any other product regulated by FDA.

II. Background

A. Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative disorders that have been identified in humans and a number of animal species (e.g., cattle, sheep, goats, elk, deer, cats, and mink), but primarily in ruminants (i.e., animals that have a stomach with four compartments, such as cattle and buffalo). A TSE is characterized by a long incubation period, followed by a shorter course of neurological symptoms, followed by death (Ref. 1). Postmortem histopathology of the brain tissue from humans and animals with TSEs is characterized by a sponge-like appearance of the brain and deposits of abnormal forms of certain cell-associated proteins (normal prion proteins) in the brain.

TSEs in humans include CJD, vCJD, Gerstmann-Sträussler-Scheinker syndrome, kuru, fatal familial insomnia, and sporadic fatal insomnia (Ref. 8). Nonhuman TSEs include BSE in cattle, scrapie in sheep and goats, transmissible mink encephalopathy (TME) in mink, feline spongiform encephalopathy (FSE) in cats, and chronic wasting disease (CWD) in deer and elk (Ref. 8). Scrapie and CWD occur, and TME has occurred, in the United States. On December 23, 2003, USDA diagnosed BSE in an adult cow in the United States that had been imported from Canada. Since then, USDA has confirmed two other cases of BSE in adult cows in the United States. One cow, which was diagnosed on June 24, 2005, was born and raised in Texas. The other cow, which was diagnosed on March 15, 2006, had been on a farm in Alabama for less than a year. The Texas cow was 12 years old and the Alabama cow was determined to be more than 10 years old. Therefore, both cows were born before the 1997 ruminant feed rule was in place. USDA determined that no part of the animals entered the human food or animal feed chains.

The pathogenesis of TSEs is poorly understood. TSE agents resist complete inactivation by treatments that destroy conventional microorganisms, like bacteria and viruses. Thus, conventional microorganisms are not likely causes of TSEs (Ref. 9). The most widely accepted explanation for TSEs, the prion theory, suggests that the infectious agents of TSEs are abnormally folded forms of normal prion proteins (Refs. 10 and 11). Normal prion protein genes are found widely in nature. In mammals, normal prion proteins are primarily expressed in neurons, but also can be found in other tissues in lower concentrations, depending on the mammalian species (Ref. 12). It is not well understood how the abnormal folding of prion proteins occurs or why hosts cannot efficiently dispose of or develop immunity to these proteins.

The current lack of an antemortem diagnostic test for TSEs in either humans or animals limits surveillance

for these diseases, studies of disease pathogenesis, and other research efforts. Diagnosis is confirmed by special postmortem examination of brain tissue by identification of abnormal prion proteins in advanced stages of the disease. At earlier stages of disease development, abnormal prion proteins are undetectable in brain tissue. Presently, there are no effective treatments for TSEs, and all TSEs are invariably fatal (Ref. 1).

B. Bovine Spongiform Encephalopathy

BSE is a TSE of cattle with a long incubation period (up to 8 years or longer), most likely acquired following consumption of an animal product containing the BSE infectious agent (Refs. 13 and 14). The British Ministry of Agriculture, Fisheries and Food (now known as the Department for Environment, Food, and Rural Affairs) first recognized BSE as a distinct disease in November 1986. The clinical signs of BSE include behavioral, gait, and postural abnormalities. The disease usually presents in cattle as increased apprehension, increased reaction to sound and touch, and a swaying gait. These signs are accompanied by subtle changes in the normal behavior of the cow, such as separation from the herd while at pasture, disorientation, staring, and excessive licking of the nose or flanks. The disease progresses to stumbling and falling, and ends with seizures, coma, and death (Ref. 15).

Experiments indicate that the infectious dose for cattle is very low. One gram of homogenized brain from affected cattle caused BSE in 7 out of 10 calves fed the brain sample. Six years after oral consumption of lower doses of brain material, 3 of 15 calves fed 0.1 gram, and 1 of 15 calves fed 0.01 gram, and 1 of 15 calves fed 0.001 gram (1 mg) of brain sample had developed the disease. This experiment is ongoing (Ref. 16).

Epidemiological studies have characterized the outbreak of BSE in the United Kingdom as a prolonged epidemic in which early cases were seen simultaneously at various locations, but with all occurrences presumably due to a common point source of infection (Ref. 17). Consistent with this observation, the subsequent spread of BSE was associated with the feeding of meat-and-bone-meal from rendered BSE-infected cattle to non-infected cattle (Ref. 17). It appears likely that the BSE agent was transmitted among cattle at an increasing rate by ruminant-to-ruminant feeding until the United Kingdom ban on such practices went into effect in 1988 (Ref. 13). The United Kingdom instituted a ruminant-to-ruminant feed ban to stop the cycle of infection, restrict the geographic spread of the disease, and eliminate potential sources of new infections. Since BSE was first identified in the United Kingdom, approximately 185,000 cattle have been diagnosed with the disease there (Ref. 18). The precautionary slaughter of millions of British cows and increasingly stringent prohibitions on certain animal feeding practices appear to have slowed, but not eradicated, the BSE epidemic in the United Kingdom. In 1992 (the peak year of the epidemic), there were over 37,000 cases of BSE in the United Kingdom; in 2005, there were 225 cases (Ref. 18).

The introduction of BSE into other countries presumably originated from their import of cattle, or animal feed made with cattle material, from the United Kingdom during the BSE epidemic (Ref. 13). In addition to the United Kingdom, BSE has been detected in indigenous cattle in Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, Japan, Liechtenstein, Luxembourg, the Netherlands, Poland, Portugal, the Republic of Ireland, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United States (Ref. 19).

C. Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob Disease (CJD) is a sporadic disease of humans that exists throughout the world with an annual incidence of approximately one case per million population (Ref. 10). The highest death rates in the United States and the United Kingdom occur in individuals between the ages of 60 and 70 (Ref. 20). Death generally occurs after less than a year of progressive neurological deterioration (Ref. 10). Early symptoms typically include changes in sleeping and eating patterns, followed by inappropriate behavior and eventual dementia, lack of coordination, and myoclonic spasms. CJD is always fatal (Ref. 20). The cause of sporadic CJD is not fully understood, but genetic susceptibility may play a role (Ref. 10). CJD has been inadvertently transmitted between humans during medical treatment or diagnostic procedures via contaminated neurosurgical instruments, transplants of dura mater and corneas, and injection of pituitary extract (Ref. 10).

In April 1996, British scientists reported a previously undetected new vCJD in young patients, with symptoms somewhat different from sporadic CJD (Refs. 21 and 22). All cases of vCJD had histopathologic evidence of spongiform changes in the brain, but also showed formation of ''florid'' plaques (a core of amyloid protein with surrounding halos of vacuoles) not typically seen in other forms of CJD (Ref. 10). Clinically, vCJD usually begins with a psychiatric presentation, such as depression, anxiety, nightmares, or hallucinations. These symptoms are followed by memory impairment, then dementia in the late stages. The clinical course generally ranges from 9 months to 3 years before death occurs (Ref. 23). The probable incubation period for vCJD in humans may range from 5 to more than 20 years (Ref. 39).

Scientists have concluded that exposure to the BSE agent is the most plausible explanation for the occurrence of vCJD (Refs. 24 through 27). Monkeys (genetically the closest animal model to humans) inoculated with samples of brain from BSE-infected cattle have been found to develop a TSE that is histopathologically similar to vCJD (Ref. 28), as have mice inoculated or fed with BSE-infected tissue (Ref. 29). Studies have shown that abnormal prion proteins from vCJD patients are molecularly similar to abnormal prion proteins from BSE-infected cattle, but different from abnormal prion proteins from patients with CJD (Ref. 23). Although the exact route of exposure is not known, most scientists believe that vCJD in humans has been caused by consumption of cattle products contaminated with the agent that causes BSE (Refs. 20, 30, and 31). There is thought to be a 10- to 10,000–fold increase in the amount of infectious material needed to cause illness in humans as compared with cattle because of the species barrier, although the European Commission's Scientific Steering Committee cautioned that this range is uncertain and in an unlikely, but worst case scenario, the species barrier may not exist (Ref. 40).

As of August 2006, 162 probable and confirmed cases of vCJD have been reported in the United Kingdom (Ref. 32). In addition, there have been 15 vCJD cases in France, 3 in Ireland, 2 in the United States ,and 1 each in Canada, Italy, the Netherlands, Portugal, Japan, Spain, and Saudi Arabia (Refs. 33 through 38 and 70). The two cases in the United States, one of the three from Ireland, and the single cases from Canada and Japan are likely due to the individual's exposure to BSE in the United Kingdom (Refs. 34, 36, and 70).

The infectious dose for humans is not known. Despite widespread exposure in the United Kingdom to BSE-contaminated meat products, only a very small percentage of the exposed population has been diagnosed with vCJD to date. This may reflect a partial

species barrier to disease transmission from cattle to humans via the oral route of exposure (Ref. 40).

D. BSE Risk Assessments

1. Harvard-Tuskegee Study

In 1998, USDA asked the Harvard Center for Risk Analysis (HCRA) and the Center for Computational Epidemiology at Tuskegee University to evaluate United States measures to prevent the spread of BSE to animals and humans if it were to occur in this country. The Harvard-Tuskegee risk assessment (the Harvard-Tuskegee study determined that the United States was highly resistant to any proliferation of BSE or a similar disease (Ref. 41). The risk assessment model also demonstrated that certain new control measures could reduce the small risk even further.

The Harvard-Tuskegee study involved a probabilistic simulation model to determine the consequences of introducing BSE into the U.S. cattle population. This simulation indicated that, in a hypothetical situation in which 10 infected cattle were imported into the United States, on average only 4 new cases of BSE would arise, and the disease would be eliminated in 20 years. The Harvard-Tuskegee study determined that these new cases of BSE would most likely arise in the United States from incomplete compliance with the FDA 1997 ruminant feed rule (see section III.A.1 of this document), and also concluded that an epidemic of BSE in this country resulting from scrapie, CWD, or another TSE is unlikely.

The Harvard-Tuskegee study estimated the number of cattle infectious doses that might be available for human exposure, but it did not estimate the likelihood of human disease from this exposure because the relationship between the two is not known. According to the study, the estimated total infectivity available for human exposure from the importation of 10 infected cattle is 39 cattle infectious doses over 20 years. The Harvard-Tuskegee study determined that the greatest sources of infectivity to consumers from food are direct consumption of cattle brain and spinal cord and also meat that contains central nervous system tissue from advanced meat recovery systems. The Harvard-Tuskegee study did not address potential human exposure to the BSE agent through food, medical products for humans, or drugs for ruminants that contain ingredients of bovine origin, such as gelatin (from bovine bones and hides), heparin and surfactants (from bovine lung), insulin (from bovine pancreas), hormones (from bovine urine and serum), enzymes (from bovine intestine), or glycosphingolipids (from bovine brains).

The Harvard-Tuskegee study identified three pathways that could lead to cattle or human exposure to the BSE agent through food or feed: (1) Noncompliance with the FDA 1997 ruminant feed rule prohibiting the use of certain proteins in feed for cattle and other ruminants; (2) rendering of animals that die on the farm and use (through illegal diversion or cross-contamination) of the rendered product in ruminant feed; and (3) the inclusion of high-risk tissues from cattle, such as brain and spinal cord, in products for human oral consumption. Evaluation of potential risk mitigation measures in the study found that a prohibition against rendering of animals that die on the farm would reduce the potential cases of BSE following hypothetical exposure by 82 percent. In addition, a ban on including SRMs (defined in the study as brain, spinal cord, gut, eyes, and advanced meat recovery products without reference to age of the animals at slaughter) in human and animal food would reduce potential BSE cases in cattle by 88 percent and potential human exposure to BSE by 95 percent. The Harvard-Tuskegee study also noted the value of ensuring that low-risk cattle tissues are not cross-contaminated with high-risk tissue.

USDA recently released an updated version of the BSE risk assessment model and report, completed by HCRA (Ref. 42). USDA requested that HCRA utilize an updated risk assessment model to evaluate the impact of measures implemented after the discovery of a BSE-positive cow in Washington State in December 2003, and recommendations made by an international BSE panel. The updated risk assessment estimates that the measures adopted by USDA in January 2004 will result in a 99.6 percent (at the mean) relative reduction in potential human exposure to the BSE agent through consumption of beef and beef products.

2. USDA Surveillance Program

The USDA has led targeted BSE surveillance efforts since 1990. On June 1, 2004, in response to a recommendation from the international scientific review panel that assessed USDA's investigation into the discovery of a BSE positive cow in Washington State on December 23, 2003, USDA began an enhanced BSE surveillance effort. This effort continued to focus on the targeted subpopulation of cattle, with a goal to obtain as many samples as possible from the targeted population, to help determine whether BSE is present in the United States. Targeted cattle are defined as nonambulatory cattle; cattle exhibiting signs of a central nervous system disorder; cattle exhibiting other signs that may be associated with BSE, such as emaciation or injury; or dead cattle. To date, USDA has sampled more than 700,000 targeted cattle, only two of which were positive for BSE (Ref. 43). A detailed analysis of surveillance data obtained through March 2006 concluded that the prevalence of BSE in the United States is less than one infected animal per million adult animals (Ref. 7).

3. BSE Testing for Product Safety Purposes

No validated antemortem tests for BSE exist. The currently available postmortem tests, although useful for disease surveillance (i.e., determining the rate of disease in the population of cattle), are not appropriate as safety indicators for food, medical products for humans, or drugs for ruminants. This is due, in part, to limitations on the existing testing methods, which rely on the use of postmortem brain tissue. Experimental evidence demonstrates that, in cattle infected orally, certain potentially infective tissues (such as the distal ileum and tonsil) are the first tissues to accumulate infectivity in the incubation period and this infectivity occurs prior to any demonstrated infectivity in brain tissue (Refs. 3, 45, and 46). Therefore, tests conducted on brain tissue may not reflect accurately the potential infectivity in other tissues that develop infectivity earlier, such as the distal ileum. Development of effective safety indicators for food, medical products for humans, and drugs for ruminants will require improved understanding of the pathogenesis of the disease and improved laboratory methods.

4. BSE Infectivity via Medical Products for Humans and Drugs for Ruminants

While BSE is usually a concern identified with food safety or animal health, medical products for humans or drugs for ruminants, because of the ways they are used or come into contact with the body, provide another route for human or ruminant exposure to the BSE infectious agent. Medical products for humans and drugs for ruminants may contain or be made using a variety of cattle-derived materials. Examples of materials that are sometimes derived from cattle and that are used in, or in the manufacture of, these products include gelatin, heparin, surfactants, hormones, enzymes,

glycosphingolipids, amino acids, glycerol, detergents, blood, collagen, fetal calf serum, bovine meat, and tallow and tallow derivatives.

The route by which TSE-contaminated material is introduced into a host is an important determinant of TSE transmissibility. Animal studies have indicated that injection of a TSE agent directly into the brain or spinal cord is the most efficient route of transmission, followed by intravenous, intraperitoneal, and subcutaneous routes, and then by the oral route (Refs. 2 and 47 through 56). Topical administration on intact skin is unlikely to lead to disease transmission, but topical products presumably can cause disease if administered to skin with cuts, abrasions, or open wounds, or if administered to the eyes or other mucosal tissue (Refs. 57 through 59).

Currently, no validated method for testing products for humans and ruminants for the agent that causes BSE is available; therefore, we do not have a means of distinguishing products that contain infectious material from products that do not. End users (e.g., consumers, physicians, farmers, veterinarians) also often are not able to determine which products contain prohibited cattle materials and which products do not because such information is generally not included in product labels or labeling. For example, rendered material including brain and spinal cord may become an ingredient in a medical product for humans or a drug for ruminants, although its presence may not be indicated on the label. Furthermore, end users have no way to determine whether cattle material in these products was sourced from nonambulatory disabled cattle or from cattle that were not inspected and passed for human consumption.

Based on what is known about transmission of BSE, there is risk of occurrence of vCJD in humans and of TSE in ruminants from the use of high-risk cattle-derived materials in medical products for humans and drugs for animals. While the results from USDA's ongoing testing are reassuring and so far have identified only two additional BSE-infected cows in the United States, one cannot rule out the possibility of future discovery of additional positive animals in the United States or in a country allowed to export cattle material to the United States, or of a future introduction of BSE. To provide consistent protection across the range of FDA-regulated products, it is necessary to put in place measures to reduce further the risk of spread of BSE in cattle and the risk of vCJD in humans. These risks may be reduced by restricting the use of high-risk cattle materials in the manufacture of drugs for ruminants and medical products for humans, similar to existing restrictions for food and cosmetics.

E. Cattle Materials

This proposed rule would apply to medical products for humans and drugs for ruminants that are manufactured from or otherwise contain certain cattle material. This section discusses the reasons for FDA's decision to propose to restrict the use of such material in medical products for humans and drugs for ruminants.

1. Specified Risk Materials

This proposed rule would designate SRMs as prohibited cattle materials in medical products for humans and drugs for ruminants. Specified risk materials would be defined, consistent with the Foods IFR (69 FR 42256 at 42259 and 70 FR 53063 at 53064 through 53065; discussed in section IV.A.3 of this document) and the USDA/FSIS IFR (69 FR 1862 and 70 FR 53043; discussed in section III of this document) as the brain, skull, eyes, trigeminal ganglia (clusters of nerve cells connected to the brain that lie close to the exterior of the skull), spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia (clusters of nerve cells attached to the spinal cord that are contained within the bones of the vertebral column) of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle.

In a pathogenesis study in which cattle were orally inoculated with BSE and then one to three animals were killed and tested at sequential 4- to 6-month intervals, Wells et al. found infectivity using a mouse bioassay at 32 months postinoculation in brain, spinal cord, dorsal root ganglia, and trigeminal ganglia (Ref. 3). Unequivocal clinical disease was first observed at 38 months postinoculation. It is not known how representative these results are, given the extremely small number of cattle tested and the limitations inherent in the mouse bioassay. It also should be noted that only one animal was tested at 26 months postinoculation and no testing was performed again until 32 months postinoculation. Thus, no conclusion can be drawn as to when, in the period between 26 and 32 months postinoculation, infectivity appeared in the tested tissues. The studies will continue for several more years, using a more sensitive cattle assay, to determine if any of the tissues that initially did not appear to be infective actually contain low levels of infection (Refs. 2 through 6 and 60). Infectivity has also been found at 6 months postinoculation in distal ileum and at 10 months postinoculation in tonsils (Refs. 4 and 60).

In cattle infected with BSE under field conditions (i.e., not intentionally exposed to BSE as part of an experiment), infectivity has been found in the brain, spinal cord, and retina of the eye in animals with clinical disease (Ref. 60). The Scientific Steering Committee of the European Union (Ref. 31) has reported on the proportion of total infectivity in various tissues. They estimate that in an animal with clinical disease, approximately 64 percent of the infectivity is in the brain, 26 percent is in the spinal cord, 4 percent is in the dorsal root ganglia, 2.5 percent is in the trigeminal ganglia, and 3 percent is in the distal ileum. The eyes are estimated to contain less than 1 percent of the infectivity. In 2003, P. J. Comer and P. J. Huntly reported generally similar estimates of infectivity (i.e., 60.2 percent in brain, 24.1 percent in the spinal cord, 3.6 percent in the dorsal root ganglia, 2.4 percent in the trigeminal ganglia and 9.6 percent in the distal ileum) (Ref. 44).

Clinical cases of BSE in cattle under 30 months old are rare. For example, according to the United Kingdom's Department of Environment, Food and Rural Affairs, among the birth cohort of cattle in the United Kingdom that had the highest incidence of BSE (those born in 1987–88), cattle under 3 years old represented less than 0.16 percent of cattle with BSE (61 out of 39,140 cattle with BSE) (Ref. 61). Another report, looking at selected herds whose ages were known, found that in the first 6 months of 1989 and 1990, the BSE incidence in 2–year-old cattle (0.04 percent in 1989 and 0.05 percent in 1990) was approximately 15–fold lower than that in 3–year-old cattle (0.56 percent in 1989 and 0.86 percent in 1990), and was 45- to 75–fold lower than the incidence in 4–year-old cattle (2.83 percent in 1989 and 2.76 percent in 1990) (Ref. 62). Two-year-old cattle represented only about one-half of 1 percent of the total BSE cases in the selected herds in those 6-month periods. The incidence in 2–year-old cattle (0.01 percent) decreased considerably in 1991, presumably reflecting the fact that they were born after July 1988, when the United Kingdom instituted measures prohibiting the use of meat and bone meal in cattle feed.

We recognize that certain tissue from infected animals will be infectious a number of months before the animals exhibit clinical symptoms. However, in

BSE, as in other TSEs, the total amount of infectivity in an animal increases throughout the incubation period reaching the highest load when an animal begins to demonstrate clinical signs (Ref. 44). Because of this evidence combined with the very low incidence of clinical BSE in cattle younger than 30 months, we are proposing, consistent with the Foods IFR (69 FR 42256 at 42259) and the USDA/FSIS IFR (69 FR 1862), that brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia should be considered SRMs only in cattle 30 months and older. We include the skull and the vertebral column in the list of SRMs because, even though they have not been shown to harbor BSE infectivity, they contain tissues (i.e., brain and spinal cord) that have been shown to be infectious. We did not include, consistent with the Foods IFR (69 FR 42256 at 42259) and the USDA/FSIS IFR (69 FR 1862 at 1868), the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum as SRMs with the rest of the vertebral column because they do not contain spinal cord or dorsal root ganglia. As the science and epidemiology on this issue develop, FDA may find it necessary through future rulemaking to modify the tissues classified as SRMs and the age at which these tissues are classified as SRMs.

Based on the previously mentioned experimental evidence indicating that tonsils become infective by 10 months postinoculation and distal ileum by 6 months postinoculation (Refs. 3 and 4), we are proposing, consistent with the Foods IFR (69 FR 42256 at 42259 and 70 FR 53063 at 53064 through 53065) and USDA/FSIS IFR (69 FR 1862 and 70 FR 53043), that the tonsil and distal ileum of the small intestine of all cattle be considered SRMs.

2. Small Intestine

The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine as measured from the caeco-colic junction and progressing proximally towards the jejunum or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum. In this medical products proposed rule, we are proposing to prohibit the use of small intestine of all cattle in medical products for humans and drugs for ruminants if procedures that completely remove the distal ileum are not used. This provision is consistent with USDA (70 FR 53043) and FDA (70 FR 53063) requirements. .

3. Mechanically Separated Beef

Mechanically Separated (Species) is a standardized food defined by USDA in 9 CFR 319.5 (see section V.A of this document for the proposed definition of mechanically separated beef). The standard does not limit the amount of spinal cord and dorsal root ganglia allowed in vertebral column used to produce the product. Consequently, mechanically separated beef may contain concentrated amounts of such tissues. Because we are proposing that spinal cord, dorsal root ganglia and vertebral column be considered SRMs, we are also proposing, consistent with the USDA/FSIS and Foods IFRs (69 FR 1862 at 1866 through 1867 and 69 FR 42256 at 42259), to include mechanically separated beef as a prohibited cattle material.

4. Nonambulatory Disabled Cattle

Experience has shown that nonambulatory disabled cattle (see section V.A of this document for the proposed definition) are the population at greatest risk for harboring BSE. Surveillance data in the European Union in 2002 showed that there were 29 positive/10,000 tests for BSE among healthy-appearing cattle of all ages and 148 positive/10,000 tests for BSE among nonambulatory animals of all ages (Ref. 63). In Switzerland, sampling of particular populations of cattle revealed that BSE-positive animals were 49 to 58 times more likely to be found in the nonambulatory population than in the population selected for passive surveillance (Ref. 64). The Harvard-Tuskegee study estimated that, following importation of 10 infected cattle, a prohibition against rendering animals that die on the farm (these animals could be nonambulatory disabled) would decrease the number of new cases of BSE by 82 percent.

Because typical clinical signs of BSE cannot always be observed in nonambulatory disabled cattle, and because evidence has indicated these cattle are more likely to have BSE than apparently healthy cattle, FDA is proposing, consistent with the Foods IFR (69 FR 42256 at 42259), to include material from nonambulatory disabled cattle as prohibited cattle materials. This proposal is also consistent with USDA's requirement that all nonambulatory disabled cattle presented for slaughter be condemned (69 FR 1862 at 1870 and 1871).

5. Cattle Not Inspected and Passed for Human Consumption

Cattle that have not been inspected (see section V.A of this document for the proposed definition) are at higher risk of having BSE, as well as other diseases, because they will not have been examined by USDA for their disease status in general and potential for harboring BSE in particular. In addition, such cattle are likely to have died on the farm or en route to slaughter, and these animals are not eligible for inspection by USDA. For cattle that are inspected but not passed, a regulatory authority (USDA or other) has made a determination that they are not appropriate for use in human food (69 FR 42256 at 42259). Such a determination may be based, among other things, on evidence of a neurological disorder associated with a higher risk of BSE. Moreover, material from cattle not inspected or inspected and not passed for human consumption is prohibited from human food (69 FR 42256 at 42259). In this rulemaking, FDA is proposing to extend this prohibition to medical products for humans and drugs for ruminants. By requiring that material from cattle for use in medical products for humans and drugs for ruminants be inspected and passed for human consumption, we would minimize the risk to humans and ruminants of exposure to the agent that causes BSE.

6. Tallow and Tallow Derivatives

Tallow is an animal-derived hard fat that has been heat processed; most tallow is derived from cattle. In this proposed rule, we use the term tallow to refer only to tallow derived from cattle. Any risk of BSE transmission from tallow is a result of protein that is present as an impurity in the tallow. Taylor et al. (Refs. 65 and 66) found in rendering studies with abnormal prion protein that the prion protein did not preferentially migrate into the fat fraction, but remained with the protein fraction. Therefore, there is no reason to believe that tallow is likely to contain unusually high amounts of prion protein as a constituent of the insoluble impurities fraction that remains in tallow after rendering. Taylor et al. (Refs. 65 and 66) also reported that the various rendering processes used for tallow production in the United Kingdom were sufficient to produce tallow that did not result in infection when injected into the brains of mice, even though the starting material was highly spiked with the scrapie agent. Wilesmith et al. (Ref. 67) noted that the geographical variation in the incidence

of BSE in the United Kingdom was not consistent with the use of tallow in cattle feed and concluded that the most likely source of infection in cattle was BSE-contaminated meat and bone meal.

The World Organisation for Animal Health (OIE) (formerly the Office International des Epizooties), the international animal health standard setting body, categorizes tallow with insoluble impurities of no more than 0.15 percent as protein-free tallow and indicates that tallow that meets this standard can be safely consumed by animals, regardless of the starting materials (Ref. 68). FDA's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) considered the safety of tallow in 1998 (Ref. 69). Although members of the TSEAC indicated that tallow is a food with extremely low risk of transmitting BSE to humans or animals, they did not see a need to change FDA's recommendation that tallow not be sourced from cattle born, raised, or slaughtered in countries where BSE is known to exist.

Based on the research and the opinions noted previously that show that tallow is inherently a low risk material because of the procedures by which it is manufactured, we are proposing to permit tallow from any country to be used in medical products for humans and drugs for ruminants, as we have for human food and cosmetics (69 FR 42256 at 42260 and 42261), if it contains no more than 0.15 percent insoluble impurities regardless of the starting materials or if it otherwise complies with these regulations (e.g., made without the use of any prohibited cattle materials). We recognize that the TSEAC did not see a need to change FDA's tallow import policy, which recommended against use of tallow from cattle born, raised, or slaughtered in countries where BSE is known to exist. However, the TSEAC was not asked to provide recommendations regarding import of tallow that met our proposed requirements. We believe we are proposing a tallow standard for medical products for humans and drugs for ruminants that is consistent with statutory safety standards and the recommendations by OIE with respect to bovine-derived tallow to prevent BSE in cattle and vCJD in humans.

Distinct from tallow are tallow derivatives. These derivatives are produced by subjecting tallow to chemical processes (hydrolysis, trans-esterification, or saponification) that involve high temperature and pressure. The TSEAC considered tallow derivatives in 1998 (Ref. 69) and determined that the rigorous conditions of manufacture are sufficient to further reduce the BSE risk in tallow derivatives. In addition, the OIE also recommends that derivatives of protein-free tallow be freely traded among countries because they pose an insignificant BSE risk to animals (Ref. 68). Because we believe that tallow has negligible risk of transmitting BSE, and tallow derivatives undergo additional processing, we do not believe that tallow derivatives pose a risk of transmitting the agent that causes BSE to humans. Therefore, we are proposing, consistent with the Foods IFR (69 FR 42256 at 42261), that tallow derivatives not be considered a prohibited cattle material. FDA proposes to clarify, as in the amendments to the Foods IFR (70 FR 53063), that the ''no more than 0.15 percent insoluble impurities'' restriction for tallow does not apply to tallow derivatives.

7. Fetal Calf Serum

Current evidence suggests that cow-to-calf transmission of BSE is unlikely to occur (Refs. 14 and 46). Therefore, the serum of fetal calves is unlikely to contain any BSE infectious material, irrespective of the age of the mother. However, because fetal calf serum (FCS) is generally collected from fetuses of dairy cows culled for low milk production or for health reasons, these cows are often considerably older than 30 months. FDA believes that manufacturers commonly take appropriate steps to prevent contamination of the FCS with specified risk materials from the mother. These steps include the normal dressing procedures used in slaughter houses, consisting of removing the uterus completely from the carcass and other viscera of cows that were inspected and passed, taking it to a separate space free of prohibited cattle materials for cardiac puncture, and collecting the fetal blood in a closed collection system using aseptic technique. Other procedures could also be used to provide adequate assurance that contamination has been prevented.

8. Additional Requirements

If the agency finds that additional protections are needed for specific products or classes of products covered by applications (e.g., products with direct routes of exposure into the bloodstream or neural tissue such as injectable, ophthalmic, intranasal, or implanted FDA-regulated products), it intends to provide those protections through the application review process or through other means, such as special controls for Class II devices. The agency believes it is possible that injectable, ophthalmic, intranasal, or implanted FDA-regulated products that contain cattle material other than prohibited cattle materials and that do not have an FDA approval covering use of that material may appear to be adulterated or misbranded under certain circumstances. If the agency finds that classes of such products or specific products do not meet the applicable statutory standards, it may take action even if the products comply with the requirements in this proposed regulation.

F. Medical Products for Humans and Drugs for Ruminants That May Contain Cattle Material

1. Drugs for Humans

Under this proposed rule, drugs for humans cannot be manufactured from or otherwise contain prohibited cattle materials without written permission from FDA. For drugs subject to applications, the agency may provide additional protections through the application review process on a case-by-case basis to ensure that the products are safe and effective for their intended uses under section 505 of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 355) and safe, pure, and potent under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). For drugs not subject to applications, if the agency finds that specific products or product classes do not meet the applicable statutory standards regarding adulteration and misbranding, it may take action even if the products comply with the requirements in this proposed rule.

Many approved human drugs, as well as investigational human drugs, contain ingredients that are derived from cattle. Over the last 10 years, FDA has maintained a database that identifies these drugs and their cattle-derived ingredients. Based on the information in this database, we are aware of no approved drugs and no investigational drugs that are manufactured with cattle material that would be prohibited under this proposed rule based on the type of cattle tissue used.[1]

In addition to human drugs with approved applications, a number of human drugs are marketed without an approved application and, therefore, have not been subject to the new drug application (NDA) review process (e.g., products marketed under FDA's over-the-counter (OTC) monograph system, Active Pharmaceutical Ingredients,

[1]All manufacturers would have to ensure that any cattle material they use comes from cattle that are inspected and passed and otherwise complies with the other requirements proposed in this rule.

homeopathic preparations, or products that purport to be ''grandfathered''). Although FDA's database of these products is incomplete, some of them may contain cattle materials that would be prohibited under this proposed rule. The requirements proposed in this rulemaking apply to all drugs for humans, including those marketed without an approved application.

2. Biologics for Humans

Many biological products are manufactured with, or otherwise use, cattle-derived material because this material can provide necessary nutrients for cell growth. For example, microorganisms used for vaccine manufacture are typically grown under controlled conditions in media that may contain cattle materials. Animal-derived products used in vaccine manufacture include amino acids, glycerol, detergents, gelatin, enzymes, and blood. Cattle skeletal muscle is used to prepare broths used in certain complex media.

Many microorganisms that are difficult to grow and cells that are used to propagate viruses require serum in the growth media, which is typically derived from cattle blood. Cattle-derived materials (e.g., fetal calf serum, insulin, aprotinin, enzymes) are often used in cell culture techniques to manufacture hematological, cell, and gene-therapy products.

Manufacturers of licensed products and sponsors of investigational new drug products are currently requested to provide, in their biologics license application (BLA) or investigational new drug application (IND), information regarding the source of all bovine-derived materials used in the manufacture of their product. This information is reviewed by FDA along with other information provided in the application. SRMs are not ordinarily used in the manufacture of biological products. Biological products that are not intended for use in or on the body (e.g., in vitro diagnostics) would not be subject to the provisions of this proposed rule.

3. HCT/Ps

This proposed rule would affect all HCT/Ps. HCT/Ps are defined in part 1271 (21 CFR part 1271) as ''articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue'' (§ 1271.3(d)). Certain exceptions apply (§ 1271.3(d)(1) through (d)(7)).

HCT/Ps are regulated according to a tiered, risk-based framework. HCT/Ps meeting the criteria listed in § 1271.10 (e.g., minimally manipulated, intended for homologous use only (i.e., perform the same basic function(s) in the recipient as in the donor), not combined with a drug or device, and not having a systemic effect) are regulated solely under the authority of section 361 of the PHS Act (42 U.S.C. 264). These ''361'' HCT/Ps are required to comply only with the applicable requirements in part 1271. Premarket review is not required for such products; therefore, FDA does not review any information regarding cattle-derived material that might be used in such products. This proposed rule would ban the use of prohibited cattle material in these products, which we believe would help reduce any possible BSE transmission through the use of ''361'' HCT/Ps manufactured using cattle-derived material.

HCT/Ps that do not meet the criteria in § 1271.10 are regulated as drugs and devices under the act, and/or biological products under section 351 of the PHS Act and the act. Establishments that manufacture such HCT/Ps must comply with the requirements in subparts C and D of part 1271 in addition to all other applicable regulations, including submission of the appropriate premarketing applications, and are included in this proposed rule. Information regarding the use of cattle-derived material in the manufacture of such HCT/Ps would be submitted as part of the premarket review, giving us the opportunity to evaluate any potential for risk of BSE transmission.

4. Medical Devices for Humans

The Center for Devices and Radiological Health (CDRH) has an administrative database that FDA reviewers use to record PMA and 510(k) submissions. In 2002, FDA added an ''animal tissue flag'' to the CDRH administrative database. This ''flag'' indicates that the device contains or is manufactured with animal tissue of some kind; the species of animal tissue is not identified. The animal tissue flag has been recorded for 68 PMAs and 2,164 510(k)s. These numbers represent only devices for which PMAs or 510(k)s were filed since the animal tissue flag was added in 2002. They do not account for devices cleared or approved for marketing before that time that may contain or that may be manufactured with animal tissue.

Examples of cattle material used in devices range from high risk tissues (such as bovine pituitary extract used as a component of growth media) used in a low risk clinical setting (such as a topical application), to low risk cattle tissues (such as collagen from cattle hide or muscle) used in a high risk clinical setting (such as direct application to the central nervous system).

Premarket submissions for devices do not always include complete information about the source of animal components. In addition, not all devices are subject to premarket review, either because they are exempt from such review or because they have already been cleared or approved. FDA believes that it is important to help ensure that all devices that are intended for use in or on the body do not contain prohibited cattle materials. Examples of devices intended for use in or on the body include, but are not limited to, vascular grafts, bone fillers, lacrimal plugs, sutures, wound dressings, and heart valves (other than human heart valve allografts regulated solely under section 361 of the PHS Act). FDA has determined that the banning and recordkeeping provisions of this proposed rule are necessary to help ensure the safety of devices intended for use in or on the body. Medical devices that are not intended for use in or on the body (e.g., in vitro diagnostics, x-ray machines) would not be subject to the provisions of this proposed rule. FDA is not aware of any currently marketed device that is manufactured with cattle material that would be prohibited under this proposed rule.

5. Drugs for Ruminants

The requirements proposed in this rulemaking would cover new animal drugs for ruminants. Ruminants present the highest risk of any animals for contracting BSE from prohibited cattle materials. Because FDA has other mechanisms to restrict the extralabel use of approved human and animal drugs that contain prohibited cattle materials in ruminants (see section V.D of this document), this proposed rule would only prohibit the use of certain cattle material in drugs intended for use in ruminants.

Some drugs for ruminants may contain or be manufactured with cattle-derived materials. We are not aware of any drugs for ruminants that contain, as a component of the drug, cattle material that would be prohibited by the proposed rule. However, although the FDA animal drug database lists materials contained in drugs for animals, it does not identify materials

that are used in the manufacture of drugs for animals but that are not intended to be components of the drug (e.g., materials used in fermentation or cell culture production of drugs for animals). Because the FDA database does not contain information on materials used in the manufacture of drugs for animals, we cannot definitively conclude that no drugs for ruminants are manufactured with the use of cattle material that would be prohibited by this proposed rule. However, based on our knowledge of the processes and materials used in manufacture of drugs for ruminants, as well as the fact that very little cattle material is prohibited if sourced from cattle that were inspected and passed and were younger than 30 months old when slaughtered, we do not believe that prohibited cattle material is needed in the manufacture (through fermentation, cell culture or otherwise) of drugs for ruminants.

III. USDA/FSIS IFR

On January 12, 2004, in response to the diagnosis of BSE in a cow in the United States, USDA published a series of interim final rules, including ''Prohibition of the Use of Specified Risk Materials for Human Food and Requirements for the Disposition of Non-Ambulatory Disabled Cattle'' (69 FR 1862). The USDA/FSIS IFR declared that SRMs were inedible and unfit for food and prohibited their use as human food. It also prohibited the use of the entire small intestine of all cattle in human food. In 2005, the USDA/FSIS IFR was amended, in part, to permit use of the small intestine of all cattle in human food if appropriate procedures are used to completely remove the distal ileum (70 FR 53043). In the Foods IFR, FDA extended similar protections to FDA-regulated human food and cosmetics. (See section IV.A.3 of this document for a discussion of the Foods IFR.)

The USDA/FSIS and Foods IFRs will reduce but will not, by themselves, eliminate the use of prohibited cattle materials in domestic and imported FDA-regulated medical products for humans and drugs for ruminants. Even when excluded from human food produced in USDA-inspected establishments, prohibited cattle materials that have been denatured may leave the establishments for rendering or destruction. These materials, which previously have not been explicitly prohibited in medical products for humans and drugs for ruminants by FDA, might then be used in FDA-regulated medical products for humans and drugs for ruminants.

Under the USDA/FSIS IFR, SRMs and carcasses of nonambulatory disabled cattle are designated as inedible. However, certain products, such as gelatin and collagen (which are both covered by the provisions of this medical products proposed rule) used in FDA-regulated medical products for humans and drugs for ruminants, have traditionally been produced from cattle material deemed inedible by the USDA. Therefore, such a designation by the USDA may not be enough to preclude use of prohibited cattle materials in FDA-regulated products without additional regulation by FDA. Furthermore, some cattle are not slaughtered under continuous USDA inspection (e.g., some are sent directly to rendering without first passing inspection). Cattle material from these animals, such as brains or bones, which include SRMs, could end up as starting material for medical products for humans and drugs for ruminants. If prohibited cattle materials were unlawfully used in FDA-regulated medical products for humans and drugs for ruminants, this proposed rule if finalized would facilitate FDA's ability to use the enforcement mechanisms of the act that apply to adulterated products (e.g., seizure) to prevent human or ruminant exposure to the prohibited cattle materials.

Imported products also may contain the types of materials prohibited by the USDA, but would not fall within the scope of the USDA's import regulations either because of the nature of the products or their country of origin. Specifically, although both FSIS and USDA's Animal and Plant Health Inspection Service (APHIS) impose BSE-related prohibitions, these prohibitions collectively do not cover all FDA-regulated medical products for humans and drugs for ruminants. For example, APHIS' BSE-related restrictions on imports do not cover gelatin for human use (beyond requiring a permit) and apply only to a limited number of countries (9 CFR 94.18).

IV. FDA Actions on BSE

A. Regulations

1. FDA 1997 Ruminant Feed Rule

In the **Federal Register** of June 5, 1997 (62 FR 30936), FDA published a regulation that prohibits, with some exceptions, the use of protein derived from mammalian tissue in feed for cattle and other ruminant animals (21 CFR 589.2000). The agency published the FDA 1997 ruminant feed rule to prevent the establishment and amplification of BSE in the United States and thereby minimize any risk to animals and humans. FDA recently proposed changes to these requirements to further strengthen the rule (see section IV.A.2 of this document).

2. FDA/USDA Animal Feed ANPRM and FDA 2005 Animal Feed Proposed Rule

Following detection of BSE in an imported dairy cow in Washington State in December 2003, the Secretaries of the U.S. Departments of Agriculture and Health and Human Services announced a series of regulatory actions and policy changes to strengthen protections against the spread of BSE in U.S. cattle and against human exposure to the BSE agent. The Secretary of Agriculture also convened an international panel of experts on BSE to review the U.S. response to the Washington case and make recommendations that could provide meaningful additional public or animal health benefits.

In the **Federal Register** of July 14, 2004 (69 FR 42287), FDA and USDA's FSIS and APHIS jointly published an ANPRM to solicit comment on additional measures under consideration based on those recommendations and other factors. FDA has since received comments on the joint ANPRM, and in the **Federal Register** of October 6, 2005 (70 FR 58570), published the FDA 2005 Animal Feed proposed rule to prohibit certain material from all animal food or feed.

3. Foods IFR

In the **Federal Register** of July 14, 2004 (69 FR 42256), FDA published an IFR prohibiting the use of certain cattle material to address the potential risk of BSE in human food, including dietary supplements, and cosmetics. This rule took effect immediately upon publication. On September 7, 2005, FDA amended the Foods IFR to revise or clarify provisions with regard to: (1) Use of small intestine (see section II.E.2 of this document) (2) use of hide and hide-derived products (see section V.A of this document), (3) use of milk and milk products (see section V.A of this document), (4) source tallow for tallow derivatives (see section II.E.6 of this document), and (5) testing method cited for determining the level of insoluble impurities in tallow (see section V.C of this document). As a result, cattle materials prohibited in human food and cosmetics include SRMs, small intestine of all cattle if procedures that completely remove the distal ileum are not used, material from nonambulatory disabled cattle, material from cattle not inspected and passed for human consumption, and mechanically separated beef. SRMs include the brain,

skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older; and the tonsils and distal ileum of the small intestine of all cattle. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. This action was taken to minimize human exposure to materials that are highly likely to contain the BSE agent in cattle infected with the disease.

4. Foods Recordkeeping/Access Final Rule

In the **Federal Register** of October 11, 2006 (71 FR 59653), FDA also published a final rule to require that manufacturers and processors of human food and cosmetics that are manufactured from, processed with, or otherwise contain, material from cattle establish and maintain records sufficient to demonstrate that the food and cosmetics are in compliance with the Foods IFR. FDA believes that records documenting the absence of prohibited cattle materials in human food and cosmetics are critical for manufacturers, processors, and FDA to ensure compliance with the ban on the use of prohibited cattle materials in the Foods IFR. FDA solicited comment on the types of records that may already be available to document the absence of prohibited cattle materials in human food and cosmetics and the types of records that could be established to document the absence of prohibited cattle materials in these FDA-regulated products. The effective date of the Foods Recordkeeping/Access final rule is January 9, 2007. Until the Foods Recordkeeping/Access final rule is effective, FDA is ensuring that it can enforce the new prohibitions in the Foods IFR through the provisions in that rule requiring that FDA be given access to any existing records relevant to compliance with the ban on prohibited cattle materials.

This proposed rule for medical products for humans and drugs for ruminants is a companion to the Foods IFR and responds to the same public health concerns. This proposed rule serves as an additional safeguard to reduce human exposure to the agent that causes BSE that may be present in cattle-derived medical products for humans and drugs for ruminants that are from domestic and imported sources.

B. FDA Guidance

During the past decade, we have communicated with the public and manufacturers, applicants, importers, and processors of FDA-regulated human and animal products regarding appropriate steps to increase product safety and minimize the risk of products being contaminated with the BSE agent. Most of our communications have been in the form of letters and guidance to industry and import alerts.

- November 1992—We wrote to manufacturers of dietary supplements to alert them to the developing concern about TSEs in animals and CJD in humans and recommended that they investigate the geographic sources of any bovine and ovine material used in their products.
- December 1993—We wrote to manufacturers of drugs, biologics, and medical devices and recommended against the use of bovine-derived materials from cattle that have resided in, or originated from, BSE countries.
- August 1994—We published a notice in the **Federal Register** (59 FR 44592, August 29, 1994) entitled ''Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products.'' In the notice, we published the text of the November 1992 and December 1993 letters previously described and, in addition, the text of letters to manufacturers of FDA-regulated products for animals (August 17, 1994), and manufacturers and importers of dietary supplements and cosmetics (August 17, 1994).
- October 1994—We issued Import Alert 17–04, which allowed for the detention, without physical examination, of bulk shipments of high-risk bovine tissues and tissue-derived ingredients from BSE countries. We have updated this alert whenever APHIS has revised the list of countries in 9 CFR 94.18.
- October 1997—We published a notice of availability (62 FR 52345, October 7, 1997) of a guidance for industry entitled ''The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use.''

The rule, if finalized, will supersede prior communications that address the same issues, including the communications identified previously.

V. Description of Proposed Rule

A. Definitions

For the purposes of this regulation, we are proposing to define the terms ''prohibited cattle materials,'' ''inspected and passed,'' ''mechanically separated beef,'' ''nonambulatory disabled cattle,'' ''specified risk materials,'' ''tallow,'' ''tallow derivative,'' and ''ruminant'' (proposed §§ 300.200(a), 500.200(a), 600.16(a), 895.102(a) and 1271.470(a)). The proposed terms and definitions are the same as those used in the Foods IFR (69 FR 42256 and 70 FR 53063), except that we are now including in proposed § 500.200(a) a definition for ruminant and we have revised the definition of prohibited cattle materials as it relates to fetal calf material. We have also made minor editorial revisions to the definition of inspected and passed. The proposed definitions are consistent with definitions used by the USDA (69 FR 1862 and 70 FR 53043).

1. *Prohibited cattle materials* means specified risk materials, small intestine of all cattle if procedures that completely remove the distal ileum are not used, material from nonambulatory disabled cattle, material from cattle not inspected and passed, or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

With regard to hides and hide-derived products, we are proposing that these products not be included in the definition of ''prohibited cattle materials.'' We are proposing this exemption because cattle hide has been determined to be a tissue with negligible risk of transmitting the agent that causes BSE; the OIE recommends that it be freely traded regardless of the BSE risk status of the exporting countries. Even though we are proposing to exempt hides and hide-derived products from the provisions of this proposed rule, applicants and manufacturers would be required to take precautions to avoid cross contamination of hides and other nonprohibited cattle material with prohibited cattle material during slaughter and processing.

With regard to milk and milk products, we are proposing that these products also not be included in the definition of ''prohibited cattle materials.'' We recognize that milk and milk products present a negligible risk of transmitting the agent that causes BSE. The OIE recommends that milk and milk products be freely traded

among countries, regardless of the BSE risk status of the exporting country. In addition, the prohibitions for medical products for humans and drugs for ruminants applies to materials from cattle slaughtered on or after the effective date of the rule and is not meant to apply to milk and milk products, which come from live cattle.

2. *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

3. *Mechanically separated beef* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, USDA's regulation that prescribes the standard of identity for Mechanically Separated (Species).

4. *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

5. *Specified risk material* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle.

6. *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

7. *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

8. *Ruminant* means any member of the suborder of animals that has a stomach with four compartments (rumen, reticulum, omasum, and abomasum) through which feed passes in digestion. The suborder includes, but is not limited to, cattle, buffalo, sheep, goats, deer, elk, and antelopes.

B. Proposed Requirements for Prohibited Cattle Materials and Permission for an Exception or Alternative to These Requirements

USDA and FDA prohibit the use of SRMs, and mechanically separated beef in human food (69 FR 1862; 69 FR 42256). USDA also requires that all nonambulatory disabled cattle presented for slaughter be condemned (69 FR 1862), while FDA prohibits use of such cattle in human food (69 FR 42256). USDA and FDA permit use of the small intestine of all cattle in human food if appropriate procedures are used to completely remove the distal ileum (70 FR 53043; 70 FR 53063).

FDA imposes these prohibitions for cosmetics as well, and also prohibits material from cattle not inspected and passed in both human food and cosmetics (69 FR 42256; 70 FR 53063). To ensure that the same materials are not incorporated into other FDA-regulated products, we are now proposing to prohibit the use of these materials in, or in the manufacture of, medical products for humans and drugs for ruminants. As with human food and cosmetics, we are proposing the following five categories of material as prohibited cattle materials: (1) The small intestine from all cattle if procedures that would completely remove the distal ileum are not used, (2) SRMs, (3) mechanically separated beef, (4) material from nonambulatory disabled animals, and (5) material from cattle not inspected and passed.

Scientists believe that the human disease vCJD is likely caused by the consumption of products contaminated with the agent that causes BSE. The relationship between the agent that causes BSE and human cases of vCJD has been described previously in section II.C of this document. Consumption of contaminated material is thought to cause illness in humans, although scientific research has not determined the infectious dose (see section II.C of this document), and there is not a test that would allow screening of cattle materials or derivative products for infectious material (see section II.D of this document). Therefore, we are proposing in § 300.200(b)(1) that, except as provided in proposed § 300.200(b)(2), no human drug be manufactured from or otherwise contain prohibited cattle materials obtained from cattle slaughtered on or after the effective date of the final rule based on this proposal. We are proposing similar limitations for other products: drugs for ruminants, human biological products (including blood products) and medical devices that are intended for use in or on the body, and HCT/Ps (defined at 21 CFR 1271.3(d)) (proposed §§ 500.200(b), 600.16(b), 895.102(b), and 1271.470(b)). With regard to HCT/Ps, this proposed prohibition (proposed § 1271.470(b)) applies to use of prohibited cattle materials in the manufacture of the HCT/P rather than the manufacture of the HCT/P from prohibited cattle materials because HCT/Ps exclude animal tissues (§ 1271.3(d)(2)(vi)).

FDA is proposing to apply the requirements of this proposed rule to all products or components of products manufactured for use in the United States or imported into the United States. This proposed rule contains the basic requirements needed to provide further protection of humans and ruminants from the potential risks of BSE posed by the use of cattle material in the manufacture of these products. Additional measures that FDA determines are needed for individual products would be addressed on a case-by-case basis through the application review process. For non-application products, if the agency finds that specific products or product classes do not meet the applicable statutory standards regarding adulteration and misbranding, it may take action even if the products comply with the requirements in this proposed rule.

The provisions in this proposed rule would apply to medical products for humans and drugs for ruminants that are manufactured from or that otherwise contain material from cattle slaughtered on or after the effective date of any final rule. The restrictions would not apply to such products (including cell lines used in the manufacture of products) that use or contain materials from cattle

slaughtered before the effective date of any final rule.

The proposed rule would provide applicants and manufacturers a mechanism for requesting FDA to grant written permission for an exception or alternative to the limitations on the use of prohibited cattle materials in medical products for humans or drugs for ruminants (proposed §§ 300.200(b)(2), 500.200(b)(2), 600.16(b)(2), 895.102(b)(2), and 1271.470(b)(2)). Applicants and manufacturers that choose to request such permission would be required to submit the request in writing to the applicable FDA Center with the requisite information as detailed below. For products subject to an application or premarket notification, this written request would be required to reference the product's application number. The Center Director may permit an exception or alternative to this proposed rule's limitation on the use of prohibited cattle materials upon the submitter's request or on his or her own initiative. Including the application number of the product in a written request for products subject to applications or premarket notifications would ensure that existing applications and clearances reflect when an exception or alternative to these proposed requirements has been submitted and when an exception or alternative has been approved.

FDA expects that applicants or manufacturers may submit a request for an exception or alternative when filing a new application or premarket notification for a product containing cattle material that would be prohibited under this proposed rule. Applicants or manufacturers may also submit a request for an exception or alternative if an existing product contains prohibited cattle materials under this proposal. Although FDA believes it is unlikely that applicants or manufacturers who currently are not using prohibited cattle materials in their products will reformulate their products to include prohibited cattle materials, proposing to do so would require not only a request for an exception or alternative but also a supplement to the approved application or a new premarket notification, consistent with existing regulations.

A request for an exception or alternative to the requirements would include: (1) The reasons why an exception or alternative to the requirements is needed, (2) a description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration, (3) a description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000, and (4) any other relevant information (paragraphs (b)(2)(ii)(A) through ((b)(2)(ii)(C) and (b)(2)(ii)(E) of proposed §§ 300.200, 500.200, 600.16, 895.102, and 1271.470). For medical products for humans, the request would be required to include a description of how the requirement is not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or how such restrictions are not necessary to ensure the safety of the product (paragraph (b)(2)(ii)(D) of proposed §§ 300.200, 600.16, 895.102, and 1271.470). For drugs for ruminants, the request would be required to include either: (1) A description of how the requirements are not necessary: (i) Based on the risks of the prohibited cattle materials in the product to the target animal and the benefits of the product to the target animal and (ii) to ensure a reasonable certainty of no harm to humans from any food derived from the target animal to which the product was administered, or (2) a description of how the requirements are not necessary to ensure the safety of the product with respect to both the target animal and any food derived from the target animal to which the product is administered (proposed § 500.200(b)(2)(ii)(D)). FDA would respond to all requests in writing and could impose conditions in granting a request. FDA could also grant permission for an exception or alternative to the requirements on its own initiative based on an evaluation of the criteria described previously. A record of any exception or alternative to the requirements in paragraph (b)(1) of proposed §§ 300.200, 500.200, 600.16, 895.102, and 1271.470 that is granted by FDA would be required to be maintained by the applicant or manufacturer under the proposed recordkeeping requirements discussed in section V.E of this document.

Although FDA believes that exceptions or alternatives to the requirements of this proposed rule would be rare, the proposal would allow medical products for humans and drugs for ruminants to be manufactured from or otherwise contain prohibited cattle materials if the agency determines that the risk posed by the use of prohibited cattle materials in the product would be outweighed by the benefits of the particular product or if the agency determines that prohibiting the use of these materials would be otherwise unnecessary to ensure the safety of the product. In the case of drugs intended for use in food-producing ruminant species, the benefits of the product relate primarily to the target animal species (ruminants), whereas the risks relate to both the health of the target animal as well as the safety of the food derived from the target animal. However, the agency does not weigh the benefits of a drug to an animal against the risks of the drug to human health, but rather considers whether there is a reasonable certainty of no harm to humans from the use of the drug in animals. Therefore, the reasonable certainty of no harm standard would be applied when considering requests for exceptions or alternatives to the proposed requirements for drugs intended for use in food-producing ruminant species. In all cases, FDA intends to apply existing statutory safety standards in determining whether to grant a written request for an exception or alternative to the proposed limitations on the use of prohibited cattle materials. (See section V.E of this document for discussion.)

In the joint ANPRM, USDA's FSIS sought comment on the issue of equivalence and BSE requirements (whether the agency should consider a country's BSE risk when determining whether a country has implemented equivalent sanitary measures to those required by the United States to prevent human exposure to the BSE agent) (69 FR 42287 at 42299 and 42300). In the Foods IFR, FDA sought comment on the standards that should be applied when determining another country's BSE status, providing an exemption for ''BSE-free'' countries, and how to determine that countries meet any standards that might be developed (69 FR 42256 at 42263). FDA here again requests comment on whether and, if so, on what basis to exempt products and components of products from ''BSE-free'' countries from our respective requirements related to BSE, including those issued by this proposed rule.

Proposed §§ 211.116 and 226.60, which would be part of FDA's current good manufacturing practice (CGMP) requirements for finished pharmaceuticals for humans and ruminants and for type A medicated articles for ruminants would prohibit use of certain cattle materials, as described in proposed §§ 300.200, 500.200 and 600.16. The CGMP requirements contain the minimum methods that must be used for the manufacture, processing, packing, or holding of a drug to ensure that the drug

meets the quality and purity characteristics that it purports or is represented to possess. The CGMP requirements contained in part 211 (21 CFR part 211) apply to finished pharmaceuticals and components of finished pharmaceuticals for both humans and animals.

The CGMP requirements contained in part 226 (21 CFR part 226) apply to Type A medicated articles. Type A medicated products are intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. A Type A medicated article consists of a new animal drug(s), with or without carrier, with or without inactive ingredients. Type A medicated articles are new animal drugs, and the manufacture of a Type A medicated article requires an approved new animal drug application (21 CFR part 514).

C. Tallow and Tallow Derivatives

Tallow would be defined as ''the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues'' (proposed §§ 300.200(a)(6), 500.200(a)(6), 600.16(a)(6), 895.102(a)(6) and 1271.470(a)(6)). Tallow derivatives would be defined as any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product (proposed §§ 300.200(a)(7), 500.200(a)(7), 600.16(a)(7), 895.102(a)(7) and 1271.470(a)(7)). For the reason described in section II.K of this document, we are proposing that tallow with no more than 0.15 percent insoluble impurities and tallow derivatives would not be defined as prohibited cattle materials under this rule even when manufactured with prohibited materials (proposed §§ 300.200(a)(1), 500.200(a)(1), 600.16(a)(1), 895.102(a)(1) and 1271.470(a)(1)). (Tallow made without using prohibited cattle materials would not be subject to this purity requirement.) We are proposing that the insoluble impurities in tallow be measured by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to the AOCS Official Method Ca 3a–46 (proposed §§ 300.200(a)(6), 500.200(a)(6), 600.16(a)(6), 895.102(a)(6) and 1271.470(a)(6)). The AOCS Official Method Ca 3a–46 is currently used by the domestic tallow industry. Reference to the AOCS Official Method Ca 3a–46 in this proposed definition does not exclude use of another method. Any testing method may be used that is equivalent to the AOCS Official Method Ca 3a–46 in accuracy, precision, and sensitivity. Those wishing to use an alternate test would be responsible for determining that it is equivalent to the AOCS Official Method Ca 3a–46; it would not be necessary for FDA to approve the use of an alternate test.

Tallow that contains more than 0.15 percent insoluble impurities could be used if it complies with the proposed requirements for cattle materials in proposed § 300.200 for drugs for humans, proposed § 500.200 for drugs for ruminants, proposed § 600.16 for biological products, proposed § 895.102 for medical devices for humans that are intended for use in or on the body, and proposed § 1271.470 for HCT/Ps (e.g., made without the use of any prohibited cattle materials).

We note that, regardless of its purity level, tallow to be used in medical products for humans and drugs for ruminants would be subject to the other provisions of the act and would be adulterated if, for example, it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth (section 501(a)(2)(A) of the act)(21 U.S.C. 351(a)(2)(A)).

D. Proposed Requirements Regarding Extralabel Drug Use in Animals

In 1994, Congress enacted the Animal Medicinal Drug Use Clarification Act (AMDUCA)(Public Law 103–396). This act authorizes the extralabel use of approved animal and human drugs in animals. The act, as well as FDA regulations in part 530 (21 CFR part 530), sets out certain conditions for extralabel use and authorizes FDA to prohibit the extralabel use of approved animal or human drugs in animals. Because FDA, elsewhere in this proposed rule, would prohibit the use of certain cattle materials in drugs for ruminants only, the agency is concerned that ruminants could still be exposed to prohibited cattle materials through the extralabel use in ruminants of a drug that was approved for a nonruminant species. Also, the agency is concerned about the extralabel use in ruminants of a drug that was approved for humans to the extent an exception or alternative to these proposed requirements has been granted. Therefore, in order to prevent the intentional or unintentional use of a drug containing prohibited cattle materials in ruminants, FDA is proposing to revise § 530.41 to prohibit in ruminants the extralabel use of drugs containing prohibited cattle material and approved for use in other animals (nonruminants) or for humans (proposed § 530.41(c)).

FDA is also proposing to add new § 530.42 that would require labels for drugs prohibited from extralabel use in ruminants and described under proposed § 530.41(c) to bear or be accompanied by labeling information to communicate to the user that extralabel use in ruminants is prohibited. The proposed regulation would require label information to include the statement ''Federal law prohibits the extralabel use of this product in ruminants.'' AMDUCA and the implementing regulation at § 530.11, however, prohibit the extralabel use of an approved new animal drug or human drug in or on animal feed. Since the extralabel use of all drugs in or on animal feed is excluded from the extralabel use provisions of AMDUCA, FDA believes it is unnecessary and potentially confusing to include the previous statement only on those feed products that contain drugs described in proposed § 530.41(c). Therefore, the labeling requirement under proposed § 530.42 would apply to all products that contain drugs described in proposed § 530.41(c) except those products used in or on an animal feed. FDA intends for sponsors of approved products that would be subject to proposed § 530.42 to revise their labeling by the effective date of the final rule based on this proposal. If necessary, FDA also would have the ability under proposed § 300.200(b)(2)(iii) to impose a labeling condition on a human drug regarding the extralabel use in ruminants of that human drug if an exception or alternative is granted.

E. Proposed Recordkeeping Requirements

We are proposing that applicants and manufacturers of medical products for humans and drugs for ruminants that are manufactured from or otherwise contain material from cattle be required to establish and maintain records that demonstrate that the material from cattle meets the requirements of this proposed rule (proposed §§ 300.200(c)(1), 500.200(c)(1), 600.16(c)(1), 895.102(c)(1) and 1271.470(c)(1)). Because at this time there is no way to screen reliably for the presence of the BSE agent or for the presence of prohibited cattle materials, applicants and manufacturers of medical products for humans and drugs

for ruminants must depend on records from the suppliers of cattle material to demonstrate that their source material is free from prohibited cattle materials. Similarly, without adequate records, FDA may not know whether applicants and manufacturers of medical products for humans and drugs for ruminants have complied with the prohibitions against use of prohibited cattle materials. Therefore, under proposed §§ 300.200(c)(1), 500.200(c)(1), 600.16(c)(1), 895.102(c)(1) and 1271.470(c)(1), applicants and manufacturers of medical products for humans and drugs for ruminants that are manufactured from or otherwise contain material from cattle would be required to establish and maintain records sufficient to demonstrate that the medical products for humans and drugs for ruminants do not contain prohibited cattle materials.

1. Types of Records

For example, to satisfy the requirement in proposed §§ 300.200(c)(1), 500.200(c)(1), 600.16(c)(1), 895.102(c)(1), and 1271.470(c)(1) that records show the absence of prohibited cattle materials, applicants and manufacturers of medical products for humans and drugs for ruminants that are manufactured from or otherwise contain brain from cattle would have to establish and maintain records to demonstrate, among other things, that the cattle brain used is not from cattle over 30 months of age.

In general, we would expect that having the following types of records on FDA-regulated medical products for humans or drugs for ruminants containing cattle material would be sufficient to demonstrate that the product is not manufactured from and does not otherwise contain prohibited cattle materials:

- A signed and dated affirmation (with contact information) by a slaughter establishment that cattle material supplied by that establishment in a particular shipment does not contain prohibited cattle materials. If two or more lots of cattle material from different slaughter establishments are pooled into a final product, then having records from each slaughter establishment should be sufficient.
- For products containing tallow, records from a slaughter establishment affirming that the tallow was produced from material containing no prohibited cattle materials or records (i.e., signed, dated, with contact information) from the tallow supplier affirming that the tallow contains no more than 0.15 percent insoluble impurities (e.g., a certificate of analyses).
- For products containing fetal calf materials, records from a slaughter establishment affirming that the fetal calf material was obtained: (1) From cows that were inspected and passed and (2) using procedures that ensure that the fetal material was not contaminated with prohibited cattle materials during slaughter or processing.

Consistent with CGMP recordkeeping requirements, applicants and manufacturers who maintain documentation of compliance should maintain that information on a lot-by-lot basis. The lot-by-lot records would ensure that each time a shipment of cattle material is sent or received, there is documentation that a management official confirmed that the shipment was free of any prohibited cattle material.

We request comments on alternative recordkeeping requirements that would ensure the requirements of the proposed rule would be met. We also request comments on whether existing recordkeeping practices include the required information and, if not, what changes the proposal would necessitate. In addition, we request comment on whether the rule should specifically require certain types of records.

2. Proposed Periods for Records Retention

The following record retention time periods would be required by this proposal:

- For drugs for humans, we are proposing, consistent with our CGMP regulations for these products (§ 211.180), to require that records be retained for at least 1 year after the expiration date of the drug (proposed § 300.200(c)(2)).
- For drugs for humans lacking an expiration date, we are proposing, consistent with our CGMP regulations for these products (§ 211.180), to require that records be retained for at least 3 years after distribution of the last lot of the drug (proposed § 300.200(c)(2)).
- For drugs for ruminants other than Type A medicated articles, we are proposing, consistent with our CGMP regulations for these products (§ 211.180), to require that records be retained for at least 1 year after the expiration date of the product (proposed § 500.200(c)(2)(ii)). Because all new animal drugs are required to have an expiration date, only the proposed 1-year records retention period would apply to all drugs for ruminants.
- For Type A medicated articles intended for use in ruminants, records would be retained, consistent with our CGMP regulations for these products (§ 226.110), for at least 2 years after distribution by the manufacturer (proposed § 500.200(c)(2)(i)).
- For human biological products, we reference 21 CFR 600.12(b) for consistency with established recordkeeping periods. Records would be retained for no less than 5 years after the records of manufacture have been completed or 6 months after the latest expiration date for the individual product, whichever represents a later date (proposed § 600.16(c)(2)).
- For medical devices that are intended for use in or on the body, we reference 21 CFR 820.180(b) for consistency with established recordkeeping periods. Records would be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer (proposed § 895.102(c)(2)).
- For HCT/Ps, we reference § 1271.270(d) for consistency with established recordkeeping periods. Records would be retained for 10 years after their creation unless otherwise stated in part 1271 (proposed § 1271.470(c)(2)).

As discussed previously, records documenting the absence of prohibited cattle materials in medical products for humans and drugs for ruminants are needed to help applicants and manufacturers ensure that they meet the proposed requirements of this rulemaking and to help FDA monitor compliance. It is important for recall purposes that records be retained for the likely period of time during which the product might be used, so that FDA can assess compliance with the requirements for cause or otherwise. The proposed timeframes for retaining records reflect the likely period of time during which medical products for humans and drugs for ruminants covered by this proposed rule might be used. The proposed timeframes for retaining records are consistent with the relevant CGMP requirements in current rules. Because of the lengthy incubation period of BSE (see section II.C of this document), we are requesting comment on whether records should be required for a longer period of time than proposed in this rulemaking. This may assist with traceback and may assist applicants and manufacturers in proving that their products are not the source of BSE infection.

In the Foods Recordkeeping/Access final rule, we require that records for FDA-regulated human food and cosmetics be retained for 2 years after the date the records were created (21 CFR 189.5(c)(2) and 21 CFR 700.27(c)(2)). FDA is requiring this

timeframe for these products so that the records will be available during the entire shelf life of the products covered by that rule.

3. Location of Records

We are proposing that records be maintained at the applicant's or manufacturer's establishment or at a reasonably accessible location. Records would be considered to be reasonably accessible if they are accessible from an onsite location (proposed §§ 300.200(c)(3), 500.200(c)(3), 600.16(c)(3), 895.102(c)(3) and 1271.470(c)(3)). Electronic recordkeeping requirements for all types of FDA required recordkeeping are addressed under part 11 (21 CFR part 11). These requirements would pertain to any records that would be required by this proposed rule.

Proposed §§ 300.200(c)(4), 500.200(c)(4), 600.16(c)(4), 895.102(c)(4) and 1271.470(c)(4) provide that records required by this subpart must be readily available to FDA for inspection and copying. All the records would be required to be in English.

Because of inherent difficulties in accessing records maintained at foreign establishments, we are proposing requirements for importers of record of medical products for humans and drugs for ruminants (proposed §§ 300.200(c)(5), 500.200(c)(5), 600.16(c)(5), 895.102(c)(5) and 1271.470(c)(5)). When filing entry with the U.S. Customs and Border Protection, importers of record of a product manufactured from or otherwise containing cattle material would be required to affirm that the product for import was manufactured from or otherwise contains cattle material and affirm that the product was manufactured in accordance with proposed §§ 300.200(b), 500.200(b), 600.16(b), 895.102(b) and 1271.470(b), as applicable. If the product was manufactured from or otherwise contains cattle material, then the importer of record would be required, if requested, to provide to FDA within 5 days records that would be sufficient to demonstrate that the product was not manufactured from and does not contain prohibited cattle material. FDA expects that the content of these records would be the same as that described as being sufficient for domestic products.

FDA believes 5 days is a reasonable amount of time for the importer of record to respond while still allowing FDA sufficient time to review the documents to make an initial admissibility decision before the conditional release period for the product expires. If the importer of record fails to provide FDA with the records within 5 days, the product would be subject to detention because it would appear to be adulterated, and the owner or consignee would be afforded notice and an opportunity for hearing in accordance with section 801(a) of the act (21 U.S.C. 381).

VI. Legal Authority

FDA has the authority to take the actions proposed in this rule under various statutory provisions. These provisions include sections 201, 301, 501, 502, 505, 512, 516, 519, 701, 704, and 801(a) of the act (21 U.S.C. 321, 331, 351, 352, 355, 360b, 360f, 360i, 371, 374, and 381(a)) and sections 351, 361, and 368 of the PHS Act (42 U.S.C. 262, 264, and 271).

With respect to drugs for humans, including drugs that are biological products, FDA is proposing these regulations under the adulteration provision in section 501(a)(2)(B) of the act, and under sections 201, 505, 701(a) and (b), 704, and 801(a) of the act.

Under section 501(a)(2)(B) of the act, FDA has the authority to impose requirements necessary to ensure that drugs meet the requirements of the act with respect to identity, strength, quality, and purity. Under section 501(a)(2)(B) of the act, a drug is adulterated if: ''the methods used in, or the facilities and controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.''

FDA is proposing to amend its CGMP regulations (proposed § 211.116) to prohibit the use of certain cattle materials in human drug products and components, including biological products, as provided by proposed §§ 300.200 and 600.16. Proposed §§ 300.200 and 600.16 would require that no drug or biological product ''be manufactured from or otherwise contain prohibited cattle materials'' unless FDA has granted a request for an exception or alternative to the requirements. Proposed § 211.116 would apply to drugs, including biological products, that are directly subject to the CGMP regulations. For drugs not directly subject to the CGMP regulations, such as active pharmaceutical ingredients and source materials, section 501(a)(2)(B) of the act supports the proposed requirements in §§ 300.200 and 600.16.

As provided in proposed §§ 300.200(d) and 600.16(d), a drug or biological product that fails to comply with the requirements of §§ 300.200(b) and 600.16(b), respectively, would be adulterated under section 501(a)(2)(B) of the act. Because of the possibility of disease transmission to humans from exposure to prohibited cattle materials, prohibiting such cattle materials in drugs and biological products will help ensure that they meet the requirements of the act with respect to safety and have the identity, and meet the quality and purity characteristics they are purported or represented to possess.

Section 201(p) of the act defines a new drug to include ''[a]ny drug *** the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof ***.'' Based on the scientific data and information available to FDA regarding the possibility of disease transmission to humans from exposure to prohibited cattle materials, under this proposed rule any human drug manufactured from, or otherwise containing, prohibited cattle materials is not generally recognized as safe and effective (GRAS/GRAE), and therefore is a new drug under section 201(p) of the act.

Section 505(a) of the act requires that ''[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) [of section 505] is effective with respect to such drug.'' Under section 505 of the act, new drug applications must demonstrate that a drug is safe and effective for its intended use(s). Because of the possibility of disease transmission to humans from exposure to prohibited cattle materials, prohibiting such cattle materials in drugs will help ensure that drugs are safe for their intended use(s). Based on the scientific data and information available to FDA regarding the possibility of disease transmission to humans from exposure to prohibited cattle materials, under this proposed rule FDA would not approve an application or supplement for a drug containing prohibited cattle materials unless an exception or alternative has been granted based upon the Center Director's determination that the safety standard in section 505 of the act would still be met. In addition, under the proposed rule, a drug containing prohibited cattle materials that is

already subject to an approval would no longer be shown to be safe based on the presence of prohibited cattle materials, and would be in violation of section 505 of the act unless an exception or alternative for use of the prohibited cattle materials has been granted. Section 505 of the act also allows FDA to impose additional conditions on an application product on a case-by-case basis, should such conditions be necessary to ensure that the product meets the standard for approval set forth in section 505 of the act.

Under section 701(a) of the act, FDA is authorized to issue regulations for the act's efficient enforcement. The proposed regulations would require measures to ensure that drugs for humans, including biologics, are being manufactured, processed, packed, or held in conformity with CGMP, and to ensure that new drugs comply with section 505 of the act, which would allow for efficient enforcement of the act. Under the proposed regulations, applicants and manufacturers of drugs for humans that are manufactured from or otherwise contain material from cattle also would be required to establish and maintain records that document the absence of prohibited cattle materials in such products and have such records readily available to FDA for inspection and copying. These proposed recordkeeping requirements are also authorized under sections 501(a)(2)(B) and 505(k) of the act.

Once material is removed from cattle, we may not be able to obtain the information necessary to determine whether it is prohibited cattle material. For example, we would not know from examination of a spinal cord whether the source animal was 30 months of age or over at the time of slaughter, or whether it was inspected and passed. Because at this time there is no way to test reliably for the presence of the BSE agent or the presence of the cattle materials prohibited in proposed § 300.200, applicants and manufacturers of drugs for humans would have to depend on records from their suppliers of cattle materials to ensure that their source material does not contain any cattle materials prohibited under proposed § 300.200. Without adequate records, FDA cannot know whether applicants and manufacturers of drugs for humans have complied with the prohibitions against certain cattle materials under proposed § 300.200. Therefore, the proposed recordkeeping requirements are necessary for the efficient enforcement of these rules and authorized under section 701(a) of the act. Under proposed § 300.200(e) and 600.16(e), the failure of an applicant or manufacturer to comply with the requirements of §§ 300.200(c) and 600.16(c), respectively, would render a drug or biological product adulterated.

We are also proposing provisions relating to records regarding imported drugs for humans under sections 801(a) and 701(b) of the act. Importers of record of such a drug product manufactured from or otherwise containing cattle material would be required to affirm that such a drug product for import was manufactured from or contains cattle material, and affirm that it was manufactured in compliance with the proposed rule. If such a drug was manufactured from or otherwise contains cattle material, then importers of record would also be required, if requested, to provide records to FDA within 5 days sufficient to demonstrate compliance. Under proposed §§ 300.200(f) and 600.16(f), failure of an importer of record to comply with those requirements causes a drug for humans to appear to be adulterated.

Section 801(a) of the act provides requirements with regard to imported drugs and provides for refusal of admission into the United States of drugs for humans that appear to be adulterated. Section 701(b) of the act authorizes the Secretaries of Treasury[2] and Health and Human Services to jointly prescribe regulations for the efficient enforcement of section 801 of the act.

Because most biological products, including blood, are also drugs, the sections of the act discussed previously provide legal authority for issuing a regulation limiting the use of prohibited cattle materials in such biological products. There is, however, additional legal authority for the proposed rule's requirements with respect to biological products generally. Section 351(a)(2)(A) of the PHS Act (42 U.S.C. 262(a)(2)(A)) requires that FDA ''establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.'' Approval of a biologics license application (BLA) must be based on a demonstration that the biological product is ''safe, pure, and potent'' (section 351(a)(2)(C)(i)(I) of the PHS Act). Limiting the use of prohibited cattle materials in biological products is designed to ensure the safety, purity, and potency of such licensed biological products. Based on the scientific data and information available to FDA regarding the possibility of disease transmission to humans from exposure to prohibited cattle materials, under the proposed rule FDA would not approve a BLA or supplement for a biological product containing prohibited cattle materials unless an exception or alternative has been granted based upon the Center Director's determination that the safety standard in section 351(a)(2)(C) of the PHS Act would still be met. In addition, under the proposed rule, a biological product containing prohibited cattle materials that is already licensed would no longer be demonstrated to be safe based on the presence of prohibited cattle materials, and would be in violation of section 351(a)(1) of the PHS Act and section 505 of the act, unless an exception or alternative for use of the prohibited cattle materials has been granted. Accordingly, FDA is proposing to amend its biological product regulations to prohibit the use of certain cattle materials in biological products as provided by proposed § 600.16.

With respect to devices, FDA is proposing to issue these regulations under the adulteration provision in section 501(g) of the act, under the misbranding provision in section 502(t) of the act, and under sections 516, 519(a), 701(a) and (b), and 801 of the act.

Under section 516 of the act, FDA may issue a regulation making a device a banned device if the agency determines, on the basis of all available data and information, that a device presents an unreasonable and substantial risk of illness or injury that can not be corrected or eliminated by labeling. A banned device is deemed adulterated under section 501(g) of the act. There are several routes through which devices intended for use in or on the body have the potential to introduce the BSE agent into humans if the devices contain prohibited cattle materials. It is well documented that central nervous system tissue, including the optic nerve, carries infectivity in animals with TSEs and humans with vCJD. Infectivity has also been transmitted to animals via mucosal tissue. Finally, although transmission through intact skin is not likely, the BSE agent has the potential to be introduced into the body through cut or abraded skin. FDA has concluded, therefore, that devices intended for use in or on the body that contain prohibited cattle materials have the potential to expose recipients of those devices if the originating cattle had BSE. Although the

[2]Under the Homeland Security Act of 2002 (Public Law 107–296), the Secretary of the Treasury has delegated all relevant Customs revenue authorities to the Secretary of Homeland Security, who has, in turn, delegated them to the Commissioner of Customs and Border Protection (CBP or Customs). If finalized, we will issue this rule jointly with the Department of Homeland Security.

over all risk of exposure is low given the low rate of BSE in U.S. cattle, this risk is deemed unacceptable given the fatal nature of vCJD. The agency is not aware of any device that can be manufactured only with prohibited cattle materials; thus, there should be no benefit to the public health from the continued marketing of devices containing these materials. FDA has determined, therefore, that devices intended for use in or on the body that contain prohibited cattle materials present an unreasonable risk to health in relation to the benefit to the public health from their continued marketing. Moreover, because there is no safe way to use these devices, the risk of disease cannot be corrected or eliminated by labeling.

It is clear, based on all available data and information, that the risk of BSE exposure may be significantly reduced by banning devices intended for use in or on the body that contain prohibited cattle materials. The agency is proposing to ban such devices, therefore, in accordance with section 516 of the act. Devices already in commercial distribution or already sold to the ultimate user are not subject to this ban because FDA is not aware of any currently marketed device that contains prohibited cattle materials. Manufacturers currently are not required to maintain records that contain information about bovine materials that would be needed to identify devices that might contain such materials. In accordance with section 516 of the act and 21 CFR part 895, interested persons may request an informal hearing on the provisions of the proposed regulation with respect to medical devices within 30 days. If a request for an informal hearing is granted, the hearing will be conducted as a regulatory hearing under 21 CFR part 16.

The proposed recordkeeping requirements for devices in this proposed rule are authorized under section 519(a) of the act. Under section 519(a), the agency may, by regulation, require that manufacturers and importers establish and maintain records, make reports, and provide information that the agency determines is necessary to ensure that devices are not adulterated or misbranded and to otherwise ensure their safety and effectiveness. FDA has determined that the recordkeeping requirements in this proposed rule are necessary to ensure that devices intended for use in or on the body do not contain prohibited cattle materials and, thus, are not adulterated under section 501(g) of the act. A device for which there is a failure or refusal to furnish any material or information required under this proposed regulation would be deemed misbranded under section 502(t) of the act.

The proposed recordkeeping requirements are also authorized under sections 701(a) and (b) and 801(a) of the act. Because at this time there is no way to screen reliably for the presence of the BSE agent or the presence of the cattle materials prohibited under this proposed rule, applicants and manufacturers of medical devices would have to depend on records from their suppliers of cattle materials to ensure that their source material does not contain any prohibited cattle materials. The proposed requirements also would allow the agency to monitor compliance with the proposed ban and, therefore, are necessary for the efficient enforcement of the act, in accordance with section 701(a) of the act. Section 801(a) of the act contains requirements with regard to imported devices and provides for refusal of admission into the United States of devices that appear to be adulterated or misbranded. Section 701(b) of the act authorizes the Secretaries of the Treasury and Health and Human Services to jointly prescribe regulations for the efficient enforcement of section 801 of the act.

With respect to new animal drugs, FDA is proposing to issue these regulations under the adulteration provision in section 501(a)(2)(B) of the act and sections 512, 701(a) and (b) and 801(a) of the act. The adulteration provision in section 501(a)(2)(B) of the act provides FDA the same authority for new animal drugs as described for drugs for humans previously in this document.

FDA is proposing to amend its CGMP regulations to prohibit the use of certain cattle materials in drug products and components intended for use in ruminant animals (proposed § 211.116). Proposed § 500.200 would require that no drug product or component intended for use in ruminants ''be manufactured from or otherwise contain prohibited cattle materials.'' Proposed § 211.116 would apply to drugs that are directly subject to the CGMP regulations. For drugs for ruminants that are not directly subject to the CGMP regulations, section 501(a)(2)(B) of the act supports the proposed requirements in proposed § 500.200.

As provided in proposed § 500.200(d), a drug that fails to comply with the requirements of § 500.200(b) would be adulterated under section 501(a)(2)(B) of the act. Because of the possibility of disease transmission to ruminants from exposure to prohibited cattle materials and to humans from consuming food from animals exposed to prohibited cattle material, prohibiting such cattle materials in drugs for ruminants would help ensure that new animal drugs for ruminants meet the requirements of the act with respect to safety, and have the identity, and meet the quality and purity characteristics they are purported or represented to possess.

Section 201(v) of the act defines a new animal drug to include ''[a]ny drug intended for use for animals other than man *** the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof ***.'' Based on the scientific data and information available to FDA regarding the possibility of disease transmission to ruminants from exposure to prohibited cattle materials, under this proposed rule any drug for ruminants manufactured from or otherwise containing prohibited cattle materials is not GRAS/GRAE, and therefore is a new animal drug under section 201(v) of the act.

Section 512 of the act provides that a new animal drug is unsafe for purposes of the adulteration provisions in section 501(a)(5) and section 402(a)(2)(C)(ii) of the act (21 U.S.C. 342(a)(2)(c)(ii)) unless there is an approval of that new animal drug application in effect. For a new animal drug application to be approved, the drug must be safe and effective for its intended use(s). Based on the scientific data and information available to FDA regarding the possibility of disease transmission to humans from exposure to prohibited cattle materials, under the proposed rule FDA would not approve an application or supplement for a drug for ruminants containing prohibited cattle materials unless an exception or alternative has been granted based upon the Center Director's determination that the safety standard in section 512 of the act would still be met. In addition, under the proposed rule, a drug for ruminants containing prohibited cattle materials that is already subject to an approval would no longer be shown to be safe based on the presence of prohibited cattle materials, and would be in violation of section 512 of the act unless an exception or alternative for use of the prohibited cattle materials has been granted.

Under section 512(a)(4) and section (a)(5) of the act, extralabel use of an approved animal drug or human drug in animals is authorized if done under certain conditions set out in FDA

regulations. However, section 512(a)(4)(A) of the act also allows FDA to prohibit particular extralabel uses of an approved new animal drug. Thus, for example, a drug approved for use in treating an animal of a nonruminant species could legally be used extralabelly to treat a ruminant animal, if it meets required conditions, unless specifically prohibited. Such drugs for nonruminant animals are allowed to contain cattle materials prohibited from use in drugs for ruminants. Absent a special prohibition, these drugs also could be used in ruminants, through extralabel use, thereby providing an avenue through which ruminants could be exposed to prohibited cattle material. Any human drug for which an exception or alternative is granted could also be used extralabelly in ruminants, which could also provide another avenue through which ruminants could be exposed to prohibited cattle materials. Therefore, under section 512(a)(4)(A) of the act (for drugs for animals) and section 512(a)(5) of the act (for drugs for humans), FDA is proposing to prohibit such extralabel use in ruminants of drugs for nonruminants or for humans containing the prohibited material.

FDA is issuing the proposed labeling requirement under sections 502(a) and 201(n) of the act (21 U.S.C. 352(a) and 321(n)). Section 502(a) provides that a drug is deemed misbranded if its labeling is false or misleading in any particular. Section 201(n) provides that ''*** in determining whether the labeling *** is misleading, there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling *** fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling *** relates under the conditions of use *** as are customary or usual.'' The proposed rule would require drugs for non-ruminants that contain prohibited materials that are prohibited from extralabel use in ruminants to be labeled ''Federal law prohibits the extralabel use of this product in ruminants.'' We believe this statement is material with respect to the consequences that may result from the extralabel use of nonruminant drugs with prohibited materials in ruminants. As discussed in other sections of this preamble, the use of materials prohibited in drugs for ruminants presents a risk of BSE. Therefore, under this proposed rule, the failure to include the labeling statement on drugs for nonruminants which contain prohibited materials would render the drugs misbranded under section 502(a) of the act. Under section 701(a) of the act, FDA is authorized to issue regulations for the act's efficient enforcement. Regulations that propose measures to ensure that drugs for animals are being manufactured, processed, packed, or held in conformity with CGMP, and to ensure that they comply with section 512 of the act, allow for efficient enforcement of the act. These proposed regulations would require applicants and manufacturers of drugs for ruminants that are manufactured from or otherwise contain material from cattle to establish and maintain records that document the absence of prohibited cattle materials in such products and make such records readily available to FDA for inspection and copying. These proposed recordkeeping requirements are also authorized under sections 501(a)(2)(B) and 512(l) of the act.

Once material is removed from cattle, we may not be able to obtain the information necessary to determine whether it is prohibited cattle material. As noted previously, we would not know from examination of a spinal cord whether the source animal was over 30 months of age at the time of slaughter or whether it was inspected and passed. Because at this time there is no way to test reliably for the presence of the BSE agent or the presence of the cattle materials prohibited in proposed § 500.200, applicants and manufacturers of drugs for ruminants must depend on records from their suppliers of cattle materials to ensure that their source material does not contain any cattle materials prohibited under proposed § 500.200. Therefore, the proposed recordkeeping requirements are necessary for the efficient enforcement of the proposed rule. Under proposed § 500.200(e), the failure of an applicant or manufacturer to comply with the requirements of § 500.200(c) would render a drug for ruminants adulterated.

We are also proposing provisions relating to records regarding imported drugs for ruminants under sections 801(a) and 701(b) of the act. Importers of record of a drug for ruminants that was manufactured from or otherwise contains cattle material would be required to affirm that the drug product for import was manufactured from or contains cattle material, and affirm that it was manufactured in compliance with the proposed rule. If a drug was manufactured from or otherwise contains cattle material, then importers of record would also be required, if requested, to provide records to FDA within 5 days sufficient to demonstrate compliance. Under proposed § 500.200(f), failure of an importer of record to comply with these requirements causes a drug to appear to be adulterated. Section 801(a) of the act provides requirements with regard to imported drugs and provides for refusal of admission into the United States of drugs for ruminants that appear to be adulterated. Section 701(b) of the act authorizes the Secretaries of Treasury[3] and Health and Human Services to jointly prescribe regulations for the efficient enforcement of section 801 of the act.

FDA has invoked section 361 of the PHS Act (42 U.S.C. 264) to prevent the transmission of numerous communicable diseases, including diseases spread through certain shellfish, turtles, birds, and human tissue intended for transplantation (see 21 CFR 1240.60 (molluscan shellfish), 1240.62 (turtles), 1240.65 (parrots and other psittacine birds), and parts 1270 and 1271 (human tissue)). Recently, FDA also issued under section 361 of the PHS Act regulations designed to prevent the spread of monkeypox from African rodents to humans (21 CFR 1240.63).

Section 361 of the PHS Act provides legal authority for FDA to limit the use of prohibited cattle materials in drugs, biological products, devices, new animal drugs for ruminants, and HCT/Ps and to inspect and copy pertinent manufacturing records to ensure compliance. Section 361(a) of the PHS Act authorizes issuance and enforcement of regulations necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries or between states. Section 361(a) of the PHS Act also provides for such inspection and destruction of articles found to be so infected or contaminated as to be ''sources of dangerous infection to human beings,'' as well as other measures that may be necessary to prevent the introduction, transmission, or spread of communicable diseases from a foreign country into a State, or from one State to another State.

Because the use of prohibited cattle materials in medical products for humans and drugs for ruminants increases the risk that the agent that

[3]Under the Homeland Security Act of 2002 (Public Law 107–296), the Secretary of the Treasury has delegated all relevant Customs revenue authorities to the Secretary of Homeland Security, who has, in turn, delegated them to the Commissioner of Customs and Border Protection (CBP or Customs). If finalized, we will issue this rule jointly with the Department of Homeland Security.

causes BSE could be transmitted to humans, limiting the use of prohibited cattle materials in medical products for humans and drugs for ruminants is a needed component of our efforts to prevent the transmission and spread of TSEs including vCJD, in humans. Scientists have concluded that exposure to the BSE agent is the most plausible explanation for the occurrence of vCJD (Refs. 24 through 27). For medical products for humans, by prohibiting use of certain cattle materials, the proposed rule would reduce the risk that the BSE agent would be transmitted directly into any person through exposure to an infectious medical product. For drugs for ruminants, by prohibiting use of certain cattle materials, the proposed rule would reduce the risk that the BSE agent would be transmitted directly into any ruminant. By protecting ruminants from exposure to the BSE agent through animal drugs, the proposed rule would also prevent transmission of the BSE agent to humans who may be exposed to products containing any ruminant materials. Consistent with the authority granted by section 361 of the PHS Act to issue and enforce such regulations as are necessary to prevent communicable disease transmission from foreign countries into the United States and from one State or possession into another, this proposed rule would provide for FDA to be able to inspect and copy pertinent manufacturing records. Because at this time there is no way to screen reliably for the presence of the BSE agent or the presence of the cattle materials prohibited under this proposed rule, the requirements with respect to the maintenance, inspection, and copying of manufacturing records are directly necessary to permit FDA to enforce the other measures designed to prevent transmission of BSE.

The proposed rule contains a procedure under which FDA could permit a manufacturer an exception or alternative to the restrictions on the use of prohibited cattle materials under limited circumstances. Specifically, a manufacturer would submit a written request for an exception or alternative to the requirements by describing: (1) Why an exception or alternative is needed; (2) the implicated product, including the type of prohibited cattle material, its manufacturing and purification processes, and its route of administration; (3) the source of the prohibited cattle material including information on the location where the cattle was born, raised, and slaughtered; and (4) any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000. For medical products for humans, the written request also would include: (1) How the limitations are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or (2) how such restrictions are not necessary to ensure the safety of the product. For drugs for ruminants, the written request would also include: (1) How the requirement is not necessary: (i) Based on the risks of the prohibited cattle materials in the product to the target animal and the benefits of the product to the target animal and (ii) to ensure a reasonable certainty of no harm to humans from any food derived from the target animal to which the product is administered, or (2) how the requirement is not necessary to ensure the safety of the product with respect to both the target animal and any food derived from the target animal to which the product is administered. The relevant Center Director could also grant written permission for an exception or alternative to the proposed requirements on his own initiative, based on these same criteria.

As discussed previously, under this proposal, FDA expects that applicants or manufacturers may submit a request for an exception or alternative when filing a new application or premarket notification for a product containing prohibited cattle materials, or if an existing product contains prohibited cattle materials. Although FDA believes it is unlikely that applicants or manufacturers who currently are not using prohibited cattle materials in their products will reformulate their products to include prohibited cattle materials, proposing to do so would require not only a request for an exception or alternative but also a supplement to the approved application or a new premarket notification, consistent with existing regulations.

In considering whether an exception or alternative to requirements of this proposed rule would meet the criteria described previously and therefore be appropriate, FDA would be required to ensure that the statutory safety standards would still be met if the exception or alternative were permitted. For drugs for humans, FDA intends to apply the safety standards set forth in sections 501(a)(2)(B) and 505 of the act. Specifically, FDA would only approve a request for an exception or alternative to the proposed limitations on prohibited cattle material if, notwithstanding the exception or alternative: (1) The drug and the methods used in, or the facilities or controls used for, its manufacturing, processing, packing, or holding conform to or are operated or administered in conformity with CGMP to ensure that such drug meets the requirements of the act as to safety and (2) the drug is safe for its intended use(s).

For biological products, FDA intends to apply the safety standard provided in section 351 of the PHS Act. Specifically, FDA would only approve a request for an exception or alternative to the proposed limitations on prohibited cattle material if, notwithstanding the exception or alternative: (1) The biological product that is the subject of the application is safe and (2) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe.

For human cells, tissues, and cellular and tissue-based products and other products regulated under the authority of section 361 of the PHS Act, FDA would only approve a request for an exception or alternative to the proposed limitations on prohibited cattle material if such limitations are not necessary to prevent the introduction, transmission, or spread of TSE.

For devices, FDA intends to apply the standard in section 516 of the act. Specifically, FDA would approve a request for an exception or alternative to the proposed ban on prohibited cattle materials only if, notwithstanding the exception or alternative, the device does not present an unreasonable and substantial risk of illness or injury.

For new animal drugs, FDA intends to apply the safety standards set forth in section 512 and 501(a)(2)(B) of the act. Specifically, FDA would approve a request for an exception or alternative to the proposed limitations on prohibited cattle material only if, notwithstanding the exception or alternative: (1) The drug and the methods used in, or the facilities or controls used for, its manufacturing, processing, packing, or holding conform to or are operated or administered in conformity with CGMP to ensure that such drug meets the requirements of the act as to safety and (2) the drug is safe for its intended use(s).

VII. Effective Date and Opportunity for Public Comment

We are proposing that any final rule based on this proposal be effective 30 days after its issuance in the **Federal Register**.

Requests for an informal hearing on the proposed ban related to medical devices must be submitted by (see **DATES**).

FDA invites public comment on this proposed rule, including the proposed

effective date for any final rule issued as a result of this proposal. The comment period on this proposed rule will be 60 days. The agency will consider modifications to this proposed rule based on comments made during the comment period. Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposed rule. 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.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not an economically significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because FDA has taken regulatory action to reduce the risk of exposure to BSE in the United States and kept affected entities informed on best practices, FDA believes the proposed rule would codify current practices of most affected entities and ensure regulatory consistency across FDA-regulated products. Few entities will need to reformulate with alternative ingredients, submit a request for exception or alternative to the limitation on the use of prohibited cattle material, or cease marketing. The FDA believes most market adjustments have taken place and this rule will not have a significant economic impact on a substantial number of small entities. A few manufacturers of certain drugs prohibited from extralabel use in ruminants would incur one-time costs to add a warning statement to the product labeling. In addition, all manufacturers that use cattle material would incur minor annual incremental recordkeeping costs. Over 10 years, the annualized costs of the proposed rule range from about $235,000 to $922,000 (at a 3 percent discount rate) and from about $235,000 to $923,000 (at a 7 percent discount rate).

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Need for the Proposed Rule

The need for this rule stems from inadequate information. Consumers, physicians, farmers, and veterinarians lack the information necessary to determine whether medical products for humans or drugs for ruminants have the potential to contain materials contaminated with the agent that causes BSE.

Currently, no validated method exists for testing medical products for humans and drugs for ruminants for the agent that causes BSE; therefore, we do not have a means of distinguishing products that contain infectious material from products that do not. For example, rendered material including brain and spinal cord may become an ingredient in medical products for humans or drugs for ruminants even though its presence may not be indicated as such on the label. Furthermore, end users have no way to determine whether cattle material in these products was sourced from nonambulatory disabled cattle or from cattle that were not inspected and passed for human consumption.

Based on what is known about the transmission of BSE, there is some risk of occurrence of vCJD in humans or of BSE in ruminants from the use of certain cattle-derived materials in medical products for humans and drugs for ruminants, respectively. While the results from USDA's ongoing testing[4] are reassuring, one cannot rule out the possible future discovery of other positive animals in the United States or in a country allowed to export cattle material to the United States, or of a future introduction of BSE. To provide consistent protection across the range of FDA-regulated products, it is necessary to put in place measures to reduce further the risk of spread of BSE in cattle and the risk of vCJD in humans. This risk may be reduced by restricting the use of high-risk cattle materials in the manufacture of drugs for ruminants and medical products for humans, similar to existing restrictions for food and cosmetics.

As discussed in section IV of this document, for over a decade the FDA has taken various actions to reduce the risk of exposure to BSE in agency-regulated medical products for humans and drugs for ruminants, including: (1) Providing information (through letters to manufacturers), import alerts, and guidances to industry related to bovine materials, (2) convening TSE advisory committee meetings to provide guidance on the sourcing of certain bovine products, including gelatin, (3) encouraging companies to be aware of and to document sourcing of bovine material through letters to manufacturers of drugs, biologics, and medical devices, and through the product approval processes, and (4) recommending that manufacturers develop plans to ensure, with a high degree of certainty, that bovine and ovine materials used in their products were not from countries where BSE exists (''BSE countries'' specified by USDA's APHIS in 9 CFR 94.18) or from sheep flocks (foreign or domestic) infected with scrapie. Moreover, manufacturers who also operate in Europe have taken steps to comply with European Union TSE regulations and guidances. The agency has also taken regulatory action to decrease the likelihood of human and ruminant exposure to BSE (e.g., FDA 1997 ruminant feed rule, FDA/USDA Animal Feed ANPRM, FDA 2005 Animal Feed proposed rule, Foods IFR, and Foods Recordkeeping/Access final rule).

The agency is proposing additional regulatory action with this rule for medical products for humans and drugs for ruminants that contain certain cattle material. Existing regulations do not explicitly bar the use of prohibited cattle material for these products. By requiring that no medical product for humans or drug for ruminants be manufactured from or otherwise contain prohibited cattle materials, this proposed rule adds another safeguard to minimize human and ruminant

[4] USDA began a BSE testing program for cattle on June 1, 2004, after discovery of a case of BSE in a cow in Washington State on December 23, 2003.

exposure to cattle material that scientific studies have demonstrated could contain the BSE agent. This proposed rule is consistent with interim final rules issued by the USDA (USDA/FSIS IFR) and FDA (Foods IFR) that exclude certain cattle material from human food, including dietary supplements, and cosmetics.

B. Scope of the Proposed Rule

Both the USDA/FSIS and Foods IFRs define SRMs as: (1) Brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse process of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older, and (2) the tonsils and distal ileum of the small intestine of all cattle. The USDA/FSIS IFR: (1) Declares SRMs, mechanically separated beef, and the carcasses and parts of nonambulatory disabled cattle to be inedible and unfit for human food, and prohibits their use in human food and (2) requires that the entire small intestine of all cattle be removed and disposed of as inedible if procedures that completely remove the distal ileum are not used. The Foods IFR limits the use of prohibited cattle materials in FDA-regulated human food, including dietary supplements, and cosmetics. Prohibited cattle material includes: (1) All materials declared inedible by the USDA/FSIS IFR and (2) material from cattle not inspected and passed for human consumption. However, prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products.

This proposed rule would define SRMs consistent with both the USDA/FSIS and Foods IFRs and would define prohibited cattle materials consistent with the Foods IFR. The proposed rule would also clarify for medical products for humans and drugs for ruminants that prohibited cattle materials do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained from suppliers who follow procedures adequate to prevent contamination with SRMs.

Current industry practices and full compliance with the USDA/FSIS and Foods IFRs serve as the baseline for this proposed rule. As discussed in section IV of this document, the agency has taken various actions over 10 years to reduce the risk of exposure to the agent that causes BSE in FDA-regulated products. We believe that most affected manufacturers have taken steps to address FDA's existing recommendations regarding the use of cattle material in FDA-regulated products. Because medical products for humans and drugs for ruminants normally use edible cattle material, we assume that the prohibited materials are not widely used in the manufacture and processing of these FDA-regulated products. By determining that medical products for humans and drugs for ruminants manufactured from, or otherwise containing, prohibited cattle materials violate the act and the PHS act, this proposed rule would clarify FDA's ability to bar the use of prohibited cattle materials in medical products for humans and drugs for ruminants that would be outside the scope of other BSE regulations.

C. Costs of the Proposed Rule

We assume that the recent USDA/FSIS and Foods IFRs have already led to most market adjustments regarding prohibited cattle materials. The manufacturers of products currently using materials from the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse process of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle would presumably be able to continue to use these ingredients, but exclusively from cattle younger than 30 months of age. However, if manufacturers use cattle tonsils, the distal ileum of small intestine of cattle, or mechanically separated beef in the manufacture of medical products for humans or drugs for ruminants, they would need to reformulate with alternative ingredients, submit a request for exception or alternative to the requirements of the proposed rule, or cease marketing the products.

1. Potential Market Adjustments

To the best of our knowledge, there are only a small number of manufacturers with drugs that do not have FDA approval (such as homeopathic drugs) that may be using prohibited cattle material. We believe the recent USDA/FSIS and Foods IFRs may have led any existing manufacturers to find substitutes for prohibited materials. The agency requests information about the impact of the proposed rule on manufacturers or importers of record of drugs that are marketed without an approved application for any reason.

2. Cost of Requests for Exceptions or Alternatives to the Limitation on the Use of Prohibited Cattle Material

We estimate that very few firms would submit requests for exceptions or alternatives to the proposed rule's requirements. We estimate that those that do would spend between 60 hours and 120 hours to prepare and submit requests for exceptions or alternatives to the limitation on the use of prohibited cattle material. With an average loaded wage of $41.50, including 33 percent for benefits ($31.16 x 1.33), each request would cost from $2,500 to $5,000 (source: Bureau of Labor Statistics (BLS) National Compensation Survey: Occupational Wages in the United States, July 2002, for executive, administrative, and managerial employees). Under this proposed rule, we estimate industry would submit three requests in the first year. Depending on the time needed to prepare and submit the request, first-year costs could range from $7,500 to $15,000. Moreover, as markets adjust further, we expect manufacturers would seek and obtain alternatives to prohibited cattle material, eliminating the need for future requests for exceptions or alternatives to the requirements of the proposed rule.

3. Cost of Substitutes

Since the USDA/FSIS and Foods IFRs bar prohibited cattle material from edible rendering (i.e., processing of edible cattle waste material into marketable products such as gelatin or tallow), manufacturers of FDA-regulated human medical products for humans and drugs for ruminants using rendered material could continue to use edible rendered products.

Some companies may need to find substitutes for other prohibited cattle material used in the manufacture of medical products for humans or drugs for ruminants. Agency records suggest that, because adequate substitutes exist, it is unlikely that the proposed rule would adversely affect markets. Nevertheless, we request comment from affected manufacturers about the costs and extent of substitution.

4. Recordkeeping Requirements of the Proposed Rule

The USDA/FSIS IFR and the Foods IFR may affect the availability of prohibited cattle materials, but would not ensure that FDA-regulated medical products for humans or drugs for ruminants are free of prohibited cattle materials. Because at this time there is no way to screen reliably for the presence of the BSE agent or for the

presence of cattle materials prohibited under this proposed rule, applicants and manufacturers would have to depend on records from their suppliers of cattle materials to ensure that their source material does not contain any cattle materials prohibited under this proposal. In addition, the agency must be able to determine whether prohibited cattle materials are used in the products it regulates. Without records, FDA may not be able to determine the inspectional status or age of the source animal once cattle material is separated from its source. The proposed rule would require that applicants and manufacturers using cattle material establish and maintain records. Records must be kept at the manufacturing or processing establishment or another reasonably accessible location, and the agency's inspectors must have access to these records.

The agency also proposes that importers of record of a medical product for humans or drug for ruminants that was manufactured from or otherwise contains cattle material affirm that the product was manufactured from or otherwise contained cattle material and affirm that the product was manufactured in accordance with the requirements in this proposed rule. Upon agency request, importers of record of affected products would provide to FDA within 5 days records that are sufficient to demonstrate compliance.

a. *Number of affected establishments.* The proposed rule is expected to affect all establishments with medical products for humans or drugs for ruminants that are manufactured from, or otherwise contain cattle materials. According to 2002 Economic Census data, up to 6,195 establishments manufactured affected products. In addition, for the current good tissue practice (CGTP) final rule, the agency estimated there are about 1,300 HCT/P establishments, most of which would be considered small (69 FR 68612 at 68654 and 68674).

FDA has developed an automated system, the Operational and Administrative System for Import Support (OASIS), to process shipments of foreign products. According to a preliminary examination of OASIS data from fiscal year 2005, approximately 3,800 unique filers requested entry of FDA-regulated products into the United States. We believe, however, that the actual number of affected filers would be less than this number because some companies may specialize in imports of products such as food, dietary supplements or cosmetics that are outside the scope of this proposed rule. Nevertheless, for this analysis we assume that all filers identified by OASIS could be affected by the proposed requirements for importers of record.

As shown in table 1 of this document, about 1,280 manufacturing establishments and 3,800 importers of record could be affected by the recordkeeping requirements. The agency seeks comment on these estimates from affected entities. In addition, although we believe the Foods Recordkeeping/Access final rule accounts for the recordkeeping burden to domestic and foreign suppliers, the agency requests comment from firms supplying cattle material to manufacturers of medical products for humans or drugs for ruminants about any additional burden that may be imposed by the recordkeeping requirements of this proposed rule.

TABLE 1.—ESTIMATED NUMBER OF AFFECTED ESTABLISHMENTS

North American Industry Classification Scheme (NAICS) Code	Total Number of Establishments[1]	Estimated Percentage of Establishments Using Cattle Material[2]	Estimated Number of Affected Establishments	Percent of Establishments Considered Small[3]
325411—medicinal & botanical manufacturing	367	75	275	98
325412—pharmaceutical preparation manufacturing[4]	901	75	674	91
325414—biological product manufacturing[5]	296	85	253	96
339112, 339113, 339114, 339115—medical devices	4,631	0.25	12	98
621991—HCT/P[6]	1,302	5	65	66
Subtotal	7,497	—	1,278	92
Importers of record[7]	3,787	unknown	3,787	unknown
Total	11,284		5,065	

[1] Source: NAICS 325411, 325412, 325414, 339112, 339113, 339114, and 339115, table 4 of the 2002 Economic Census, Manufacturing, Industry Series; NAICS 621991, table 3 in 69 FR 68612 at 68654. Number of importers of record estimated from FDA's OASIS data for FY 2005.

[2] Percentages are based on FDA's knowledge of products containing cattle material. We assume equal distribution of affected products across all establishments.

[3] The SBA considers entities small if they have less than: (1) 750 employees for NAICS 325411 and 325412, (2) 500 employees for NAICS 32514, 339112, 339113, 339114, and 339115, or (3) $9.0 million in revenues or receipts for NAICS 621991. Because the Economic Census uses different size categories than SBA, this analysis treats establishments in NAICS 325411 and 325412 with less than 999 employees as small. The agency previously estimated that about 66 percent of establishments in NAICS 621991 are small (table 14 in 69 FR 68612 at 68674).

[4] We assume that cattle materials are used by 70 percent of establishments primarily manufacturing products for veterinary use and 75 percent of establishments primarily manufacturing products for human use. Source for the total number of establishments and the number of establishments manufacturing each primary product class: Tables 4 and 5 of the 2002 Economic Census, Manufacturing, Industry Series, EC02–311–325412.

[5] We assume that cattle materials are used by 70 percent of establishments primarily manufacturing products for veterinary use and 90 percent of establishments primarily manufacturing products for human use. Source for the total number of establishments and the number of establishments manufacturing each primary product class: Tables 4 and 5 of the 2002 Economic Census, Manufacturing, Industry Series, EC02–311–325412.

[6] We assume that from 1 to 5 percent of establishments use cattle materials.

[7] Based on FY 2005 data in OASIS; equals the total number of unique filers for all FDA-regulated products.

b. *Recordkeeping costs.* Manufacturers of medical products for humans and drugs for ruminants would need to establish and maintain appropriate records that document the absence of prohibited cattle materials in their products. This would require that manufacturers verify and maintain records from suppliers of any material derived from cattle. In addition, when filing an entry with the U.S. Customs and Border Protection, importers of record of affected products would be required to affirm that the product was manufactured from or otherwise contains cattle material and affirm that the product was manufactured in accordance with the proposed provisions. If a product was manufactured from, or otherwise contains, cattle material, then importers of record would also be required, if requested, to provide within 5 days records sufficient to demonstrate that the product was not manufactured from and does not contain prohibited cattle material.

As noted previously, we believe that most entities have taken steps to address the sources of cattle materials. Moreover, the CGMP and CGTP regulations covering medical products for humans and drugs for ruminants require that procedures be in place for purchasing controls. We believe, however, that some affected manufacturers currently may not keep adequate records and might incur minor incremental recordkeeping costs. For this analysis, therefore, we assume that, on average, all affected small manufacturers may spend slightly more than 1 hour annually to maintain records. Similarly, we assume that, on average, all affected large manufacturers may spend slightly less than 3 hours annually to maintain records. With a loaded wage rate of $33.00 (source: Bureau of Labor Statistics (BLS) National Compensation Survey: Occupational Wages in the United States, July 2002, adding 33 percent overhead for a computer programmer), small and large manufacturers might incur about $45 and $90, respectively, to ensure full compliance with the requirements to establish and maintain records.

This rule would require importers of record of affected products to affirm that the product was manufactured from or otherwise contains cattle material and affirm that the product was manufactured in accordance with the proposed provisions. Although the marginal burden of each affirmation would be negligible, we believe the cumulative burden might cause smaller importers to spend about the same level of effort as small manufacturers (i.e., $45 annually). In contrast, we assume that larger importers might spend about 5 times the level of effort as small importers (i.e., $225 annually). Because the agency lacks information about importer size, we include a range of possible recordkeeping costs for this analysis. Table 2 shows the estimated recurring recordkeeping costs for this proposed rule. However, because there is some uncertainty about the new burden that might be imposed and the number of firms that might be affected by this proposed rule, the agency requests comment from affected manufacturers and importers of record on this estimated recordkeeping burden.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN BY INDUSTRY AND ESTABLISHMENT SIZE[1]

NAICS or Type of Industry	Small		Large		Total Cost ($)
	Number Affected	Cost ($)	Number Affected	Cost ($)	
325411	269	12,100	7	600	12,700
325412	615	27,700	58	5,200	32,900
325414	243	11,000	9	800	11,800
339112, 339113, 339114, 339115	11	500	0	0	500
621991 (HCT/P)	43	1,900	22	2,000	3,900
Subtotal	1,182	53,200	96	8,600	61,800
	Lower Bound (i.e., 3,787 small importers)		Upper Bound (i.e., 3,787 large importers)		
Importers of record[2]		170,400		852,100	170,400 to 852,100
Total					232,200 to 913,900

[1] Totals may not multiply or sum due to rounding.

[2] Because we lack data on the size of affected importers of record, we calculate the lower and upper bounds for these costs, assuming that either all firms are small or all firms are large.

5. Labeling Costs for New Animal Drugs Prohibited from Extralabel Use

Manufacturers of new animal drugs prohibited from extralabel use in ruminants would need to add a warning statement to the product labeling. We estimate manufacturers of about eight animal products would spend from $1,600 to $6,400 to change the product labeling and file a labeling supplement for each affected product. Costs are based on discussions with experts in the Center for Veterinary Medicine and are presented in table 3 of this document.

TABLE 3.—ESTIMATED ONE-TIME COSTS OF LABELING CHANGES AND FILING A SUPPLEMENT

Cost Component	Hours/ Establishment	Total Cost [1] ($)
Regulatory review and approval	3 to 12	1,000 to 3,980
Artwork [2]	-	4,000
Manufacturing	4 to 12	570 to 1,710
Inventory Loss [3]	-	6,640 to 40,000
Supplement preparation and Submission	2 to 5	660 to 1,660
Total Cost [4]		12,870 to 51,350

[1] We calculated using a loaded wage rate for regulatory review and filing a supplement of $41.50, for manufacturing changes $17.80. Source: BLS National Compensation Survey: Occupational Wages in the United States, July 2002, adding 33 percent for benefits.

[2] We assume the unit costs for artwork are $500 per product.

[3] We assume the unit costs for inventory loss range from $830 to $5,000 per product.

[4] Totals may not add or multiply due to rounding.

6. Summary of the Costs for the Proposed Rule

Few firms will incur one-time costs for requests for exceptions or alternatives to the limitation on the use of prohibited cattle material. In addition, manufacturers of about eight animal products prohibited from extralabel use in ruminants would incur one-time costs to add a warning statement to the product labeling. All firms that use cattle material or import products that do would incur annual incremental costs for additional recordkeeping. The total one-time costs range from $20,400 to $66,300; annual costs range from $232,200 to $913,900. The total annualized costs of this option range from $234,600 to $921,700 (at a 3 percent discount rate) and from $235,100 to $923,300 (at a 7 percent discount rate) over 10 years. These costs are summarized in table 4 of this document.

TABLE 4.—SUMMARY OF TOTAL COMPLIANCE COSTS [1]

One-Time Cost	Lower Bound ($)	Upper Bound ($)
Requests for exception or alternative	7,500	15,000
Change labeling and file a supplement	12,900	51,300
Total one-time cost	20,400	66,300
Annual recordkeeping cost	232,200	913,900
Total annualized cost at 3 percent	234,600	921,700
Total annualized cost at 7 percent	235,100	923,300

[1] Numbers may not add due to rounding.

D. Benefits of the Proposed Rule

1. Reduced Risk of Exposure to BSE Infectivity

USDA analyses to date have found the United States is highly resistant to the introduction or establishment of BSE and predict that even if BSE were introduced into the United States, only a small amount of potentially BSE-contaminated tissues would reach the human food supply and be available for consumption (Ref. 41). Moreover, their models predict that implementation of a ban on specified risk materials (e.g., spinal cords, brains, vertebral columns) from both human food and animal feed would reduce substantially the very low risk of additional BSE cases in cattle and the potential human exposure to infectivity from meat and meat products.

None of these risk assessments considered the potential exposure to BSE infectivity from certain FDA-regulated products containing bovine material. The risks of exposure to BSE infectivity from medical products for humans and drugs for ruminants are unknown, but the risk of transmission could be higher than for foods and cosmetics assuming the presence of BSE infectivity. For example, the routes of administration for some of these products (such as from injectable and implantable products) are associated with higher risk than oral or topical exposure associated with foods and cosmetics. This proposed rule covers products not included in the recent USDA or Foods IFRs and would ensure that medical products for humans and drugs for ruminants containing cattle material meet specific requirements designed to reduce the risk of human exposure to BSE-infective materials.

The proposed rule would decrease the likelihood of human and ruminant exposure to BSE in several ways. First, this rule would provide additional regulatory protection, beyond existing rules, by making clear that prohibited cattle material cannot be used in FDA-regulated medical products for humans or drugs for ruminants. Second, because affected products manufactured from or otherwise containing prohibited cattle materials would be adulterated and the failure of an importer of record to comply with applicable reporting requirements creates the appearance of adulteration under section 801, the proposed rule would clarify FDA's ability to bar importation of medical products for humans or drugs for ruminants that contain prohibited cattle materials. For example, imported products may contain the types of materials prohibited by FDA, but may not fall under the scope of USDA's import restrictions.

2. Value of the Potential Reduction of Human Illness

The public health benefit of this proposed rule is the value of the reduction in the risk of the human illness associated with exposure to the agent that causes BSE. If we define the baseline risk as the expected annual number of cases of vCJD per year, then the annual benefits of barring prohibited cattle materials from use in affected products would be: (baseline annual cases of vCJD—annual cases of vCJD under FDA PR) x (value of preventing a case of vCJD).

We do not know the baseline expected annual number of cases, but based on the epidemiology of vCJD in the United Kingdom, we anticipate much less than one case of vCJD per year in the United States. Because the proposed rule would reduce rather than eliminate risk of exposure to BSE infectious materials, the reduction in the number of cases would be some fraction of the expected number. FDA uses the concept of the Value of a Statistical Life (VSL) in order to describe the value of preventing a case

of vCJD. This term refers to the sum of risk reductions expected in a population exposed to small changes in risk. It has no application to identifiable individuals or large reductions in risk. Most recent studies suggest values ranging from about $1 million to $10 million. In recent rulemakings, we have used $5 million and $6.5 million as the value of a statistical life, and we believe it is reasonable to use a similar VSL to value the cases of vCJD avoided.

E. Summary of the Potential Costs and Benefits of the Proposed Rule

The total annualized costs of this proposed rule range from $234,600 to $921,700 (at a 3 percent discount rate) and from $235,100 to $923,300 (at a 7 percent discount rate) over 10 years. By reducing exposure to potentially infectious materials, the requirements of the proposed rule would provide an additional safeguard against a case of vCJD occurring in humans if cattle infected with BSE were used in the manufacture or processing of medical products for humans and drugs for ruminants. We are unable to estimate the value of this potential reduction in the risk of cases of vCJD, even though we estimate the value of avoiding one death at $5.8 million. Nonetheless, we believe the potential benefits of the proposed rule justify the small costs of the rule.

F. Regulatory Options Considered

For this proposed rule, FDA considered three regulatory options:

(1) *No new regulation.* By definition, no costs and benefits are associated with the baseline. As noted previously, USDA and FDA actions to date would reduce, but not eliminate, the availability and use of prohibited cattle materials in domestic and imported FDA-regulated medical products for humans and drugs for ruminants. Without regulation, FDA would not be explicitly barring the use of prohibited cattle materials that could potentially contain the BSE infectious agent.

(2) *Propose a rule that (i) bars the use of prohibited cattle materials in medical products for humans and drugs for ruminants, unless a request for exception or alternative to the limitation of the use of prohibited cattle material has been granted, and (ii) requires establishment, maintenance, and access to records demonstrating that no medical products for humans or drugs for ruminants are manufactured from or otherwise contain prohibited cattle material.* These would be the minimum basic requirements, and would not preclude the imposition of additional measures through the application review process or other means if FDA determined that they were necessary for ensuring the safety of individual products on a case-by-case basis.

This is the regulatory option selected. The agency believes that this is the best option to meet its goal of minimizing human and ruminant exposure to materials that scientific studies have demonstrated are likely to contain the BSE agent in cattle infected with the disease. The ban on use of prohibited materials would eliminate exposure to the highest risk animals and the majority of the infectivity in an animal infected with the BSE agent. This option would provide reasonable balance by explicitly barring from medical products for humans and drugs for ruminants the use of potentially infectious materials already deemed unfit for foods by USDA and FDA and by imposing minimal regulatory burden. The agency must be able to determine that the products it regulates contain no prohibited cattle materials. Applicants and manufacturers must depend on records to ensure that affected products do not contain any cattle materials prohibited under the proposal. Without recordkeeping requirements, FDA may not be able to determine the source or age of cattle material once it is separated from the animal. In addition, records would allow the agency to determine the inspectional status of the source animals.

(3) *Propose a rule that, in addition to the requirements listed in option (2), bars the use in medical products for humans and drugs for ruminants of all neural material from cattle from countries with a high or medium risk of BSE if the cattle were slaughtered when over 6 months old, unless a request for exception or alternative to the requirements has been granted.* This approach would be more consistent with recommendations of OIE and would add an additional layer of protection to that provided by option (2). This alternative would put an additional burden on those parts of the affected industries that source cattle materials from such countries and do not already have procedures in place ensuring and documenting compliance with the requirement.

Compared to the preferred option (2), we believe this alternative would impose higher costs on, at most, a small segment of the affected industries. In fact, we know of no manufacturers of U.S. licensed or approved medical products for humans and drugs for ruminants for which this alternative would impose any additional burdens beyond those imposed under option (2), because they do not source such materials from such countries. However, we also believe it would not provide significant additional risk reduction because so few animals diagnosed with BSE are younger than 3 years old. For example, cattle born in 1987/1988 in the United Kingdom had the highest incidence of BSE, with over 39,000 cattle diagnosed with BSE. Among those animals, cattle under 3 years old represented only 0.16 percent of cattle with BSE (61 cattle). Once controls were put in place, that number decreased, so that of animals born after 1996, all cattle diagnosed with BSE have been 3 years old or older.

G. Regulatory Flexibility Analysis

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. The FDA believes this proposed rule will not have a significant economic impact on a substantial number of small entities and requests comment.

The proposed rule may affect entities classified in several industries including Medicinal & Botanical Manufacturing (NAICS 325411), Pharmaceutical Preparation Manufacturing (NAICS 325412), Biological Product (Except Diagnostic) Manufacturing (NAICS 325414), Surgical and Medical Instrument Manufacturing (NAICS 339112), Surgical Appliance and Supplies Manufacturing (NAICS 339113), Dental Equipment and Supplies Manufacturing (NAICS 339114), Ophthalmic Goods Manufacturing (NAICS 339115), and Blood and Organ Banks (NAICS 621991). The Small Business Administration (SBA) regards an entity as small based on the number of employees or the average annual receipts. The size standards are: (1) 750 employees for NAICS categories 325411 and 325412, (2) 500 employees for NAICS categories 325414, 339112, 339113, 339114 and 339115, and (3) $9.0 million average annual receipts for NAICS 621991. The U.S. Census gathers employment data for establishments by NAICS and uses size categories that differ from those of the SBA for NAICS 325411 and 325412. For this regulatory flexibility analysis, therefore, we consider entities in these NAICS categories with less than 999 employees to be small. Using these size standards, 2002 Census data, and the CGTP final rule (69 FR 68612 at 68654 and 68674),

over 90 percent of these establishments would be considered small (see tables 1 and 2 of this document). However, the agency lacks information on the types of importers of record that might be affected by the proposed rule. Agency data on filers that import FDA-regulated products into the United States does not include the size of the importer of record. Therefore, for the initial regulatory flexibility analysis, we assume that all affected importers of record would be classified as small. The agency requests comment on this assumption.

We believe requirements in this proposed rule must apply to all entities, regardless of size. No new skills are needed. To meet the proposed requirements, those applicants and manufacturers of medical products for humans or drugs for ruminants manufactured from or otherwise containing cattle tonsils, the distal ileum of the small intestine of cattle, or mechanically separated beef might need to switch to an alternative source material, submit a request for exception or alternative to the limitation on prohibited cattle material in this proposed rule, or cease marketing the products. We expect that other affected manufacturers would continue to use age-specific cattle material from animals under 30 months of age. A few small entities could incur from $2,500 to $5,000 for each request submitted unless a request for exception or alternative to requirements of the proposed rule has already been granted. In addition, manufacturers of about eight animal products prohibited from extralabel use in ruminants would incur costs of between $1,600 and $6,400 per product to add a warning statement to the product labeling and file a labeling supplement. Although it is uncertain if any small entities will incur these costs, Table 5 shows that for very small establishments with less than 10 employees these one-time costs would equal less than 1.6 percent of the average annual value of shipments. Moreover, for all small establishments in each of the affected industries, the one-time costs to revise labeling or prepare a request for exception or alternative to requirements of the proposed rule would equal no more than 0.15 percent of the average annual value of shipments.

TABLE 5. POTENTIAL DIRECT COMPLIANCE COSTS OF THE PROPOSED RULE AS A PERCENTAGE OF AVERAGE ANNUAL SHIPMENTS FOR AFFECTED ESTABLISHMENTS WITH LESS THAN 10 EMPLOYEES.[1]

NAICS Category	Average Annual Shipments Per Establishment ($)	Compliance Costs as a Percentage of Average Annual Shipments[2]		
		Recordkeeping ($45 Per Establishment)	Labeling Revision ($6,500 Per Product)	Request for Exception or Alternative ($5,000 Per Request)
325411, Medicinal and botanical manufacturing	1,059,245	0.004%	0.6%	0.5%
325412, Pharmaceutical preparation manufacturing	1,656,743	0.003%	0.4%	0.3%
325414, Biological product (except diagnostic) manufacturing	1,057,862	0.004%	0.6%	0.5%
339112, Surgical and medical instrument manufacturing	610,138	0.007%	1.0%	0.8%
339113, Surgical appliance and supplies manufacturing	618,207	0.007%	1.0%	0.8%
339114, Dental equipment and supplies manufacturing	396,666	0.011%	1.6%	1.3%
339115, Ophthalmic goods manufacturing[3]	1,121,083	0.004%	0.6%	0.4%
621991 Blood and organ banks	4,281,172	0.001%	0.1%	0.1%

[1] Source: Table 4 of 2002 Economic Census for NAICS 325411, 325412, 325414, 339112, 339113, 339114, 339115, and 621991.

[2] Averages based on the sum of data for establishments with 1 to 4 employees and 5 to 9 employees. For establishments with 1 to 4 employees, recordkeeping costs equal less than 0.02 percent of average annual shipments for all NAICS categories. It is unlikely that entities with 1 to 4 employees would incur compliance costs for a labeling revision or a request for exception or alternative to requirements of the proposed rule. Nevertheless, for these smallest entities, as a percentage of average annual shipments, a labeling revision equals less than 2.6 percent and a request for exemption or alternative equals less than 2.0 percent for all NAICS categories.

[3] No information for establishments with 1 to 4 employees.

Besides the one-time compliance burden that a few small entities might incur, most affected small manufacturers would incur minor new compliance costs for recordkeeping. For small manufacturers and small importers of record, these annual costs would equal about $45, a negligible amount for even the smallest entities. Table 5 shows that these incremental recordkeeping costs for establishments with less than 10 employees would equal less than 0.02 percent of their average annual value of shipments.

FDA lacks the data required to estimate the number of requests, the distribution of one-time labeling costs, and the new annual recordkeeping burden on small entities. We anticipate, however, that the potential costs might represent a very small percentage of their annual revenues and would not be a significant economic impact on affected small entities. Nevertheless, the agency requests detailed data on small business impacts from affected firms.

As discussed in section VIII. F. of this document, FDA considered other regulatory options. The proposed rule is the least burdensome option that meets FDA's goal of minimizing human and ruminant exposure to materials that scientific studies have demonstrated are

likely to contain the BSE agent in cattle infected with the disease.

IX. Paperwork Reduction Act Analysis

This proposed rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501 3520). A description of these provisions is given below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on the following topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants

Description: As discussed previously in this document, we are proposing to prohibit the use of certain cattle material in medical products for humans and drugs for ruminants because of the risk of BSE and related human disease. The rulemaking contains reporting and recordkeeping requirements that are subject to review by OMB.

Reporting. Under proposed §§ 300.200(b)(2)(i) and (b)(2)(ii) for drugs for humans, 500.200(b)(2)(i) and (b)(2)(ii) for drugs for ruminants, 600.16(b)(2)(i) and (b)(2)(ii) for biological products, 895.102(b)(2)(i) and (b)(2)(ii) for human medical devices that are intended for use in or on the body, and 1271.470(b)(2)(i) and (b)(2)(ii) for HCT/Ps, applicants and manufacturers could request permission for an exception or alternative to the requirements in proposed §§ 300.200(b)(1), 500.200(b)(1), 600.16(b)(1), 895.102(b)(1), and 1271.470(b)(1) that no medical product for humans or drug for ruminants be manufactured from or otherwise contain prohibited cattle materials obtained from cattle slaughtered on or after the effective date of the regulation. To obtain written permission from FDA for an exception or alternative to the requirements, applicants and manufacturers would send a written request to the director of the Center having jurisdiction over the relevant product. Any request would contain the following:

- A statement of the reasons why an exception or alternative is needed;
- A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;
- A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under ? 589.2000;
- A description, if applicable, of how the requirements that pertain to their product in proposed §§ 300.200(b)(1), 600.16(b)(1), 895.102(b)(1), or 1271.470(b)(1) are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product, or how such restrictions are not necessary to ensure the safety of the product;
- A description, if applicable, of: (1) How the requirements that pertain to their product in proposed § 500.200(b)(1) are not necessary: (i) Based on the risks of the prohibited cattle materials in the product to the target animal and the benefits of the product to the target animal and (ii) to ensure a reasonable certainty of no harm to humans from any food derived from the target animal to which the product was administered, or (2) how such restrictions are not necessary to ensure the safety of the product with respect to both the target animal and any food derived from the target animal to which the product is administered; and
- Any other relevant information.

As discussed in the Analysis of Impacts (see section VIII of this document), we estimate that a request for an exception or alternative to the requirements would take between 60 and 120 hours to complete and submit to FDA. For purposes of this information collection analysis, we estimate, as indicated in table 6 of this document, that each request would take approximately 120 hours. We estimate that only three requests would be submitted to FDA in the first year by applicants and manufacturers of medical products for humans and drugs for ruminants because only a small number of such products are currently manufactured with cattle materials that would be prohibited under this rule. We expect that applicants and manufacturers would seek, and obtain, alternatives to prohibited cattle materials, eliminating the need for future requests for an exception or alternative to the requirements of the proposed rule. We request comments on our estimates of the number of exception/alternative requests, the time for preparation and submission of the request, and the likelihood of requests beyond the first year after the rule would be in effect.

Under proposed §§ 300.200(c)(5), 500.200(c)(5), 600.16(c)(5), 895.102(c)(5), and 1271.470(c)(5), when filing entry with the U.S. Customs and Border Protection, importers of record of a medical product for humans or a drug for ruminants that was manufactured from, or otherwise contains, cattle material would be required to affirm that the product was manufactured from or otherwise contained cattle material and affirm that the product was manufactured in accordance with the requirements in this proposed rule. If a product was manufactured from, or otherwise contains, cattle material, then importers of record would also, if requested, have to provide to FDA within 5 days records that would be sufficient to demonstrate that the product was not manufactured from, and does not contain, prohibited cattle material. As discussed in the Analysis of Impacts (see section VIII of this document), we estimate that 3,787 importers of record would be subject to this affirmation and potential record submission and that it would take each of them between 1 and 5 hours annually to process. For purposes of this information collection analysis, we estimate, as indicated in table 6 of this document, that this proposed provision would take each importer of record approximately 2.5 hours annually to process.

Under proposed § 530.42, FDA would require that labels for drugs prohibited from extralabel use in ruminants by proposed § 530.41(c) bear or be accompanied by the statement ''Federal law prohibits the extralabel use of this product in ruminants.'' This labeling statement is not subject to review by OMB because it is ''originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)) and, therefore, does not constitute a ''collection of information'' under the PRA.

Recordkeeping. Under proposed §§ 300.200(c), 500.200(c), 600.16(c), 895.102(c), and 1271.470(c), applicants and manufacturers of medical products for humans and drugs for ruminants that are manufactured from, or otherwise contain, material from cattle would be required to establish and maintain records demonstrating that their products have not been manufactured from and do not otherwise contain, prohibited cattle materials and make such records available to FDA for inspection and copying. These proposed requirements are necessary because, once materials are separated from an animal, it may not be possible without records to know the following: (1) Whether the cattle material contains SRMs, (2) whether the material was sourced from an animal that was inspected and passed for human consumption, (3) whether the material was sourced from a nonambulatory disabled animal, and (4) whether the product contains mechanically separated beef. Under the proposed rule, applicants and manufacturers must retain records the varying periods of time consistent with the applicable CGMP or CGTP requirements (e.g., for drugs for humans, it would be at least 1 year after the expiration date of the drug; for drugs for humans lacking an expiration date, it would be at least 3 years after distribution of the last lot of the drug). These records would be required to be maintained at the applicant's or manufacturer's establishment or another reasonably accessible location.

Recordkeeping requirements currently exist for applicants and manufacturers of medical products for humans and drugs for ruminants under FDA's CGMP and CGTP regulations. For drugs and biological products for humans and drugs for ruminants, these requirements are at part 210 (21 CFR part 210) and part 211 (CGMP), and the information collection requirements for these regulations are already approved by OMB under OMB Control Number 0910–0139 until September 30, 2008. For blood and blood components, these requirements are at 21 CFR part 606 (CGMP), and the information collection requirements for these regulations are already approved by OMB under OMB Control Number 0910–0116 until December 31, 2008. For Type A medicated articles, these requirements are at part 226 (CGMP), and the information collection requirements for these regulations are already approved by OMB under OMB Control Number 0910–0154 until December 31, 2007. For medical devices for humans, these requirements are at 21 CFR part 820 (CGMP/quality system regulations), and the information collection requirements for these regulations are already approved by OMB under OMB Control Number 0910–0073 until September 30, 2007. For HCT/Ps, these requirements are at part 1271, subpart D (CGTP regulations), and the information collection requirements for these regulations are already approved by OMB under OMB Control Number 0910–0559 until November 30, 2007. In accordance with the previously mentioned CGMP and CGTP regulations, applicants and manufacturers of medical products for humans and drugs for ruminants would be responsible for maintaining records regarding use of cattle materials in, or in the manufacture of, their products. However, FDA estimates that, in accordance with this rulemaking, applicants and manufacturers would expend a small amount of additional effort to comply with the proposed recordkeeping requirements. FDA has determined, as indicated in table 7 of this document, that there are 1,278 applicants and manufacturers of a medical product for humans or drug for ruminants that would be responsible for recordkeeping. This would include verifying records and storing records that contain information on sources of cattle materials that are to be used in medical products for humans and drugs for ruminants. As discussed in the Analysis of Impact (see section VIII of this document), we estimate that this recordkeeping burden will be about 1 to 3 hours per year. For purposes of this document, we estimate, as indicated in table 7, that this burden would take about 2 hours/year. Therefore, the total annual burden will be 2 hrs x 1,278 = 2,556 hours, as shown in table 7 of this document.

Description of Respondents: Applicants and manufacturers of medical products for humans and drugs for ruminants that are manufactured from, or otherwise contain, material from cattle slaughtered on or after the effective date of the regulation.

TABLE 6.—ESTIMATED REPORTING BURDEN [1]

21 CFR Section	Number of Respondents	Frequency per Response	Total Responses	Hours per Response	Total Hours
300.200(b)(2)(i) and (b)(2)(ii), 500.200(b)(2)(i) and (b)(2)(ii), 600.16(b)(2)(i) and (b)(2)(ii), 895.102(b)(2)(i) and (b)(2)(ii), and 1271.470(b)(2)(i) and (b)(2)(ii)	3	1	3	120	360
300.200(c)(5), 500.200(c)(5), 600.16(c)(5), 895.102(c)(5), and 1271.470(c)(5)	3,787	1	3,787	2.5	9,467.5
Total					9,827.5

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 7.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
300.200(c), 500.200(c), 600.16(c), 895.102(c), and 1271.470(c)	1,278	1	1,278	2	2,556

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection to OMB (see **DATES** and **ADDRESSES**).

X. Environmental Impact Analysis

FDA has carefully considered the potential environmental effects of this proposed rule (i.e., ban use of prohibited cattle materials in medical products for humans and drugs for ruminants, unless a request for exception or alternative to the requirements has been granted) and of two possible alternative actions: (1) No action and (2) in addition to the requirements proposed in this rule, ban use in medical products for humans and drugs for ruminants of all neural material from cattle from countries with a high or medium risk of BSE if the cattle were slaughtered when over 6 months old, unless a request for exception or alternative to the requirements has been granted. In doing so, the agency focused on the environmental impacts of its action, specifically, disposal of unused cattle byproducts (e.g., dead animals and slaughter byproducts) that can no longer be used in medical products for humans or drugs for ruminants after the rule becomes effective.

The environmental assessment (EA) considered each of the alternatives in terms of the need to provide maximum reasonable protection of human health without resulting in a significant impact on the environment. The EA considered environmental impacts related to landfill, incineration, composting, and land burial. The additional waste that might result from the selected action would be an extremely small amount compared to the total amount of waste generated by the cattle industry.

The agency has concluded that the proposed rule will not have a significant impact on the human environment and that an environmental impact statement is not required. FDA's finding of no significant impact (FONSI) and the evidence supporting that finding, contained in an EA prepared under 21 CFR 25.40, may be seen in the Dockets Management Branch (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday. FDA invites comments and submission of data concerning the EA and FONSI.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

XII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

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List of Subjects

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 226

Animal drugs, Animal feeds, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

21 CFR Part 300

Drugs, Incorporation by reference, Prescription drugs.

21 CFR Part 500

Animal drugs, Animal feeds, Cancer, Incorporation by reference, Labeling, Packaging and containers, Polychlorinated biphenyls (PCBs).

21 CFR Part 530

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

21 CFR Part 600

Biologics, Incorporation by reference, Reporting and recordkeeping requirements.

21 CFR Part 895

Administrative practice and procedure, Incorporation by reference, Labeling, Medical devices.

21 CFR Part 1271

Biologics, Drugs, Human cells and tissue-based products, Incorporation by reference, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR parts 211, 226, 300, 500, 530, 600, 895, and 1271 as follows:

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

2. Section 211.116 is added to subpart F to read as follows:

§ 211.116 Use of cattle material.

Use of certain cattle material in drug products and components is prohibited as provided by §§ 300.200, 500.200, and 600.16 of this chapter.

PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES

3. The authority citation for 21 CFR part 226 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360b, 371, 374.

4. Section 226.60 is added to subpart C to read as follows:

§ 226.60 Use of cattle material.

Use of certain cattle material in Type A medicated articles for ruminants is prohibited as provided by § 500.200 of this chapter.

PART 300—GENERAL

5. The authority citation for 21 CFR part 300 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360b, 361, 371, 381; 42 U.S.C. 264, 271.

6. Section 300.200 is added to subpart C to read as follows:

§ 300.200 Prohibited cattle materials.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321) apply to such terms when used in this section. The following definitions also apply:

(1) *Prohibited cattle materials* means specified risk materials; small intestine of all cattle except as provided in paragraph (b)(3) of this section; material from nonambulatory disabled cattle; material from cattle not inspected and passed; or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

(2) *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated beef* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, the U. S. Department of Agriculture's (USDA's) regulation that prescribes the standard of identity for Mechanically Separated (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk materials* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from the AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(b) *Requirements.* (1) At a minimum, except as provided in paragraph (b)(2) of this section, no drug intended for use in humans shall be manufactured from, or otherwise contain, prohibited cattle materials obtained from cattle slaughtered on or after [effective date of final rule].

(2) The requirements in paragraph (b)(1) of this section with respect to prohibited cattle materials shall not apply if FDA grants written permission for an exception or alternative to such requirements.

(i) To obtain written permission from FDA, you must send a written request to the Director of the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. For a drug subject to an application, your written request must reference its application number. The Center Director may also grant written permission for an exception or alternative to the requirements in paragraph (b)(1) of this section on his own initiative and shall base such a determination on an evaluation of the criteria described in paragraph (b)(2)(ii) of this section. You must maintain a record of any exception or alternative to the requirements in paragraph (b)(1) of this section that is granted by FDA, in accordance with paragraph (c) of this section.

(ii) A written request for an exception or alternative to the requirements in paragraph (b)(1) of this section must include, for each applicable product:

(A) A statement of the reasons why an exception or alternative is needed;

(B) A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;

(C) A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000 of this chapter;

(D) A description of how the requirements in paragraph (b)(1) of this section are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or how such restrictions are not necessary to ensure the safety of the product; and

(E) Any other relevant information.

(iii) FDA shall respond in writing to all requests for an exception or alternative to the requirements and may impose conditions in granting any such request.

(3) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records.* (1) Applicants and manufacturers of a drug that is manufactured from, or otherwise contains, cattle material must establish and maintain records sufficient to demonstrate that the material is not manufactured from, and does not contain, prohibited cattle materials.

(2) Records must be retained for at least 1 year after the expiration date of the drug or, for drugs lacking an expiration date, at least 3 years after distribution of the last lot of the drug.

(3) Records must be retained at the applicant's or manufacturer's establishment or at a reasonably accessible location. Records are considered to be reasonably accessible if they are accessible from an onsite location.

(4) Records required by this section must be readily available to FDA for inspection and copying. All the records must be in English.

(5) When filing entry with the U.S. Customs and Border Protection, the importer of record of a drug manufactured from, or otherwise containing, cattle material must affirm that the drug was manufactured from, or otherwise contains, cattle material and must affirm that the drug was manufactured in accordance with this section. If a drug was manufactured from, or otherwise contains, cattle material, then the importer of record must, if requested, provide to FDA within 5 days records that are sufficient to demonstrate that the drug is not manufactured from, and does not contain, prohibited cattle material.

(d) A human drug that is not in compliance with the requirements of paragraph (b) of this section is adulterated under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)).

(e) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section renders a drug adulterated under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)).

(f) Failure of an importer of record to comply with the requirements of paragraph (c) of this section causes a drug to appear to be adulterated under section 801(a) of the act (21 U.S.C. 381(a)).

(g) A human drug that is a new drug and that is not in compliance with the requirements of paragraph (b) of this section is in violation of section 505 of the act (21 U.S.C. 355).

(h) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section is a violation of section 301(e) of the act (21 U.S.C. 331(e)).

(i) Any person who violates the requirements of paragraph (b) or (c) of this section shall be subject to the penalties provided in section 368 of the Public Health Service Act (42 U.S.C. 271).

PART 500—GENERAL

7. The authority citation for 21 CFR part 500 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 353, 360b, 371, 381; 42 U.S.C. 264, 271.

8. New subpart F is added to part 500 to read as follows:

Subpart F—Substances Prohibited From Animal Drugs

§ 500.200 Prohibited cattle materials in drugs intended for use in ruminants.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321) apply to such terms when used in this section. The following definitions also apply:

(1) *Prohibited cattle materials* means specified risk materials; small intestine of all cattle except as provided in paragraph (b)(3) of this section; material from nonambulatory disabled cattle; material from cattle not inspected and passed; or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

(2) *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated beef* means a meat food product that is finely

comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, the U. S. Department of Agriculture's (USDA's) regulation that prescribes the standard of identity for Mechanically Separated (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column or metabolic conditions.

(5) *Specified risk materials* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(8) *Ruminant* means any member of the suborder of animals that has a stomach with four compartments (rumen, reticulum, omasum, and abomasum) through which feed passes in digestion. The suborder includes, but is not limited to, cattle, buffalo, sheep, goats, deer, elk, and antelopes.

(b) *Requirements*. (1) At a minimum, except as provided in paragraph (b)(2) of this section, no drug intended for use in ruminants shall be manufactured from, or otherwise contain, prohibited cattle materials obtained from cattle slaughtered on or after [effective date of final rule].

(2) The requirements in paragraph (b)(1) of this section with respect to prohibited cattle materials shall not apply if FDA grants written permission for an exception or alternative to such requirements.

(i) To obtain written permission from FDA, you must send a written request to the Director of the Center for Veterinary Medicine, 7519 Standish Place, Rockville, MD 20855. For a drug intended for use in ruminants that is subject to a new animal drug application, your written request must reference its application number. The Center Director may also grant written permission for an exception or alternative to the requirements in paragraph (b)(1) of this section on his own initiative and shall base such a determination on an evaluation of the criteria described in paragraph (b)(2)(ii) of this section. You must maintain a record of any exception or alternative to the requirements in paragraph (b)(1) of this section that is granted by FDA, in accordance with paragraph (c) of this section.

(ii) A written request for an exception or alternative to the requirements in paragraph (b)(1) of this section must include, for each applicable product:

(A) A statement of the reasons why the exception or alternative is needed;

(B) A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;

(C) A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000 of this chapter;

(D)(*1*) A description of how the requirements in paragraph (b)(1) of this section are not necessary:

(*i*) Based on the risks of the prohibited cattle materials in the product to the target animal and the benefits of the product to the target animal; and

(*ii*) To ensure a reasonable certainty of no harm to humans from any food derived from the target animal to which the product was administered; or

(*2*) A description of how the requirements in paragraph (b)(1) of this section are not necessary to ensure the safety of the product with respect to both the target animal and any food derived from the target animal to which the product is administered; and

(E) Any other relevant information.

(iii) FDA shall respond in writing to all requests for an exception or alternative to the requirements and may impose conditions in granting any such request.

(3) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records*. (1) Applicants and manufacturers of a drug intended for use in ruminants that is manufactured from, or otherwise contains, any cattle material must establish and maintain records sufficient to demonstrate that the material is not manufactured from, and does not contain, prohibited cattle materials.

(2) The following record retention periods apply:

(i) Records for a Type A medicated article intended for use in ruminants that is manufactured from, or otherwise contains, any cattle material must be retained for at least 2 years after distribution by the manufacturer.

(ii) Records for a drug intended for use in ruminants, other than a Type A medicated article, that is manufactured from, or otherwise contains, any cattle material must be retained for at least 1 year after the expiration date of the drug.

(3) Records must be retained at the applicant's or manufacturer's establishment or at a reasonably accessible location. Records are considered to be reasonably accessible if they are accessible from an onsite location.

(4) Records required by this section must be available to FDA for inspection and copying. All the records must be in English.

(5) When filing entry with the U.S. Customs and Border Protection, the importer of record of a drug intended for

use in ruminants that was manufactured from, or otherwise contains, cattle material must affirm that the drug was manufactured from, or otherwise contains, cattle material and must affirm that the drug was manufactured in accordance with this section. If a drug was manufactured from, or otherwise contains, cattle material, then the importer of record must, if requested, provide to FDA within 5 days records that are sufficient to demonstrate that the drug is not manufactured from, and does not contain, prohibited cattle material.

(d) A drug intended for use in ruminants that is not in compliance with the requirements of paragraph (b) of this section is adulterated under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)).

(e) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section renders a drug intended for use(s) in ruminants adulterated under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)).

(f) Failure of an importer of record to comply with the requirements of paragraph (c) of this section causes a drug intended for use(s) in ruminants to appear to be adulterated under section 801(a) of the act (21 U.S.C. 381(a)).

(g) A drug intended for use in ruminants that is a new animal drug and that is not in compliance with the requirements of paragraph (b) of this section is in violation of section 512 of the act (21 U.S.C. 360b).

(h) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section is in violation of section 301(e) of the act (21 U.S.C. 331(e)).

(i) Any person who violates the requirements of paragraph (b) or (c) of this section shall be subject to the penalties provided in section 368 of the Public Health Service Act (42 U.S.C. 271).

PART 530—EXTRALABEL DRUG USE IN ANIMALS

9. The authority citation for 21 CFR part 530 is revised 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; 42 U.S.C. 264, 271.

10. Section 530.41 is amended by removing the word ''for'' from the section heading, paragraph (a) introductory text, and paragraph (b) and adding in its place the word ''from''; and by adding paragraph (c) to read as follows:

§ 530.41 Drugs prohibited from extralabel use in animals.

* * * * *

(c) Drugs that contain prohibited cattle material as defined in §§ 300.200(a)(1) and 500.200(a)(1) of this chapter are prohibited from extralabel use in ruminants.

* * * * *

11. Section 530.42 is added to subpart E to read as follows:

§ 530.42 Labeling requirements for new animal drugs prohibited from extralabel use in animals.

(a) The labeling of any approved new animal drug that is prohibited from extralabel use in ruminants by § 530.41(c) must bear the statement ''Federal law prohibits the extralabel use of this product in ruminants.''

(b) Failure to comply with the labeling requirements in paragraph (a) of this section renders a drug misbranded under section 502(a) of the act.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

12. The authority for 21 CFR part 600 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264, 271, 300aa–25.

13. Section 600.16 is added to subpart B to read as follows:

§ 600.16 Prohibited cattle materials.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321), section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), and § 600.3 apply to such terms when used in this section. The following definitions also apply:

(1) *Prohibited cattle materials* means specified risk materials; small intestine of all cattle except as provided in paragraph (b)(3) of this section; material from nonambulatory disabled cattle; material from cattle not inspected and passed; or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

(2) *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated beef* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, the U. S. Department of Agriculture's (USDA's) regulation that prescribes the standard of identity for Mechanically Separated (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk materials* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(b) *Requirements.* (1) At a minimum, except as provided in paragraphs (b)(2) and (b)(4) of this section, no biological product intended for use in humans shall be manufactured from, or otherwise contain, prohibited cattle materials obtained from cattle slaughtered on or after [effective date of final rule].

(2) The requirements in paragraph (b)(1) of this section with respect to prohibited cattle materials shall not apply if FDA grants written permission for an exception or alternative to such requirements.

(i) To obtain written permission from FDA, you must send a written request to the Director of the Center for Biologics Evaluation and Research (see § 600.2 for mailing address) or the Director of the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers lane, Rockville, MD 20857, depending on the Center with primary jurisdiction over the product. Your written request must reference its application number. The Center Director may also grant written permission for an exception or alternative to the requirements in paragraph (b)(1) of this section on his own initiative and shall base such a determination on an evaluation of the criteria described in paragraph (b)(2)(ii) of this section. You must maintain a record of any exception or alternative to the requirements in paragraph (b)(1) of this section that is granted by FDA, in accordance with paragraph (c) of this section.

(ii) A written request for an exception or alternative to the requirements in paragraph (b)(1) of this section must include, for each applicable product:

(A) A statement of the reasons why an exception or alternative is needed;

(B) A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;

(C) A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000 of this chapter;

(D) A description of how the requirements in paragraph (b)(1) in this section are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or how such restrictions are not necessary to ensure the safety of the product; and

(E) Any other relevant information.

(iii) FDA shall respond in writing to all requests for an exception or alternative to the requirements and may impose conditions in granting any request.

(3) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(4) Biological products that are not intended for use in or on the body (e.g., in vitro diagnostics) are not subject to the requirements of paragraph (b)(1) of this section.

(c) *Records.* (1) Establishments that manufacture a biological product intended for use in or on the body that is manufactured from, or otherwise contains, cattle material must establish and maintain records sufficient to demonstrate that the material is not manufactured from, and does not contain, prohibited cattle materials.

(2) Records must be retained consistent with § 600.12(b).

(3) Records must be retained at the manufacturer's establishment or at a reasonably accessible location. Records are considered to be reasonably accessible if they are accessible from an onsite location.

(4) Records required by this section must be available to FDA for inspection and copying. All the records must be in English.

(5) When filing entry with the U.S. Customs and Border Protection, the importer of record of a biological product intended for use in or on the body that was manufactured from, or otherwise contains, cattle material must affirm that the product was manufactured from, or otherwise contains, cattle material and must affirm that the product was manufactured in accordance with this section. If a product was manufactured from, or otherwise contains, cattle material, then the importer of record must, if requested, provide to FDA within 5 days records that are sufficient to demonstrate that the product is not manufactured from, and does not contain, prohibited cattle material.

(d) A biological product that is a drug and that is not in compliance with the requirements of paragraph (b) of this section is adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and not safe, pure, and potent under section 351 of the PHS Act (42 U.S.C. 262).

(e) Failure of an applicant or manufacturer of a biological product that is a drug to comply with the requirements of paragraph (c) of this section renders such product adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and not safe, pure, and potent under section 351 of the PHS Act (42 U.S.C. 262).

(f) Failure of an importer of record to comply with the requirements of paragraph (c) of this section causes a biological product to appear to be adulterated under section 801(a) of the act (21 U.S.C. 381).

(g) A biological product that is a new drug and that is not in compliance with the requirements of paragraph (b) of this section is in violation of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and section 351 of the PHS Act (42 U.S.C. 262).

(h) A biological product that is a device and that is not in compliance with the requirements of paragraph (b) of this section is adulterated under section 501(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(g)) and in violation of section 351 of the PHS Act (42 U.S.C. 262).

(i) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section is a violation of section 301(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(e)).

(j) Any person who violates the requirements of paragraph (b) or (c) of this section shall be subject to the penalties provided in section 368 of the PHS Act (42 U.S.C. 271).

PART 895—BANNED DEVICES

14. The authority citation for 21 CFR part 895 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 360f, 360h, 360i, 371, 381; 42 U.S.C. 264, 271.

15. Section 895.102 is added to subpart B to read as follows:

§ 895.102 Prohibited cattle materials.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321) apply to such terms when used in

this section. The following definitions also apply:

(1) *Prohibited cattle materials* means specified risk materials; small intestine of all cattle except as provided in paragraph (b)(3) of this section; material from nonambulatory disabled cattle; material from cattle not inspected and passed; or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more that 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

(2) *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated beef* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, the U. S. Department of Agriculture's (USDA's) regulation that prescribes the standard of identity for Mechanically Separated (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk materials* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months or older and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(b) *Requirements.* (1) At a minimum, except as provided in paragraph (b)(2) of this section, no medical device for humans that is intended for use in or on the body shall be manufactured from, or otherwise contain, prohibited cattle materials obtained from cattle slaughtered on or after [effective date of final rule].

(2) The requirements in paragraph (b)(1) of this section with respect to prohibited cattle materials shall not apply if FDA grants written permission for an exception or alternative to such requirements.

(i) To obtain written permission from FDA, you must send a written request to the Director of the Center for Devices and Radiological Health, 9200 Corporate Blvd., Rockville, MD 20850. For a device subject to premarket approval or premarket clearance, your written request must reference its application number. The Center Director may also grant written permission for an exception or alternative to the requirements in paragraph (b)(1) of this section on his own initiative and shall base such a determination on an evaluation of the criteria described in paragraph (b)(2)(ii) of this section. You must maintain a record of any exception or alternative to the requirements in paragraph (b)(1) of this section that is granted by FDA, in accordance with paragraph (c) of this section.

(ii) A written request for an exception or alternative to the requirements in paragraph (b)(1) of this section must include, for each applicable product:

(A) A statement of the reasons why an exception or alternative is needed;

(B) A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;

(C) A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000 of this chapter;

(D) A description of how the requirements in paragraph (b)(1) of this section are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or how such restrictions are not necessary to ensure the safety of the product; and

(E) Any other relevant information.

(iii) FDA shall respond in writing to all requests for an exception or alternative to the requirements and may impose conditions in granting any such request.

(3) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records.* (1) Applicants and manufacturers of a medical device that is intended for use in or on the body that is manufactured from, or otherwise contains, cattle material must establish and maintain records sufficient to demonstrate that the material is not manufactured from, and does not contain, prohibited cattle materials.

(2) Records must be retained consistent with § 820.180(b) of this chapter.

(3) Records must be retained at the applicant's or manufacturer's establishment or at a reasonably accessible location. Records are considered to be reasonably accessible if they are accessible from an onsite location.

(4) Records required by this section must be available to FDA for inspection and copying. All the records must be in English.

(5) When filing entry with the U.S. Customs and Border Protection, the

importer of record of a medical device intended for use in or on the body that was manufactured from, or otherwise contains, cattle material must affirm that the device was manufactured from, or otherwise contains, cattle material and must affirm that the device was manufactured in accordance with this section. If a device was manufactured from, or otherwise contains, cattle material, then the importer of record must, if requested, provide to FDA within 5 days records that are sufficient to demonstrate that the device is not manufactured from, and does not contain, prohibited cattle material.

(d) A medical device that is intended for use in or on the body that is not in compliance with the requirements of paragraph (b) of this section is adulterated under section 501(g) of the act (21 U.S.C. 351(g)).

(e) Failure of an applicant or manufacturer of a medical device that is intended for use in or on the body to comply with the requirements of paragraph (c) of this section renders the device misbranded under section 502(t) of the act (21 U.S.C. 352(t)).

(f) Failure of an importer of record to comply with the requirements of paragraph (c) of this section causes a medical device that is intended for use in or on the body to appear to be adulterated under section 801 of the act (21 U.S.C. 381).

(g) Failure of an applicant or manufacturer to comply with the requirements of paragraph (c) of this section is a violation of section 301(e) of the act (21 U.S.C. 331(e)).

(h) Any person who violates the requirements of paragraph (b) or (c) of this section shall be subject to the penalties provided in section 368 of the Public Health Service Act (42 U.S.C. 271).

PART 1271—HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

16. The authority citation for 21 CFR part 1271 continues to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

17. Part 1271 is amended by adding new subpart G to read as follows:

Subpart G—Prohibited Cattle Materials

§ 1271.465 Applicability.

The provisions set forth in this subpart are applicable only to HCT/Ps described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264) and the regulations in this part, and to the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the Federal Food, Drug, and Cosmetic Act, or are biological products regulated under section 351 of the PHS Act (42 U.S.C. 262), are not subject to the regulations set forth in this subpart. Such products are subject to the applicable regulations for biological products and for drugs or devices.

§ 1271.470 Prohibited cattle materials.

(a) *Definitions.* The following definitions apply to this section:

(1) *Prohibited cattle materials* means specified risk materials; small intestine of all cattle except as provided in paragraph (b)(3) of this section; material from nonambulatory disabled cattle; material from cattle not inspected and passed; or mechanically separated beef. Prohibited cattle materials do not include tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products. Prohibited cattle materials also do not include materials obtained from fetal calves of cows that were inspected and passed, as long as the materials were obtained by procedures adequate to prevent contamination with specified risk materials.

(2) *Inspected and passed* means that the material is from an animal that has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time the animal was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated beef* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses, that meets the specifications contained in 9 CFR 319.5, the U. S. Department of Agriculture's (USDA's) regulation that prescribes the standard of identity for Mechanically Separated (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk materials* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled ''Insoluble Impurities'' (AOCS Official Method Ca 3a–46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a–46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave., Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(b) *Requirements.* (1) At a minimum, except as provided in paragraph (b)(2) of this section, no HCT/P intended for use in humans shall be manufactured using, or otherwise contain, prohibited cattle materials obtained from cattle slaughtered on or after [effective date of final rule].

(2) The requirements in paragraph (b)(1) of this section with respect to prohibited cattle materials shall not apply if FDA grants written permission for an exception or alternative to such requirements.

(i) To obtain written permission from FDA, you must send a written request to the Director of the Center for Biologics Evaluation and Research (see § 600.2 of this chapter for mailing address). The Center Director may also grant written permission for an exception or alternative to the requirements in paragraph (b)(1) of this section on his own initiative and shall base such a determination on an evaluation of the criteria described in

paragraph (b)(2)(ii) of this section. You must maintain a record of any exception or alternative from the requirements in paragraph (b)(1) of this section that is granted by FDA, in accordance with paragraph (c) of this section.

(ii) A written request for an exception or alternative to the requirements in paragraph (b)(1) of this section must include, for each applicable product:

(A) A statement of the reasons why an exception or alternative is needed;

(B) A description of the product, including the type of prohibited cattle materials used in its manufacturing, its manufacturing and purification processes, and its route of administration;

(C) A description of the source of the prohibited cattle materials, including information on the location where the cattle were born, raised, and slaughtered, and any other information relevant to the likelihood of the cattle having ingested material prohibited under § 589.2000 of this chapter;

(D) A description of how the requirements in paragraph (b)(1) of this section are not necessary based on the risks of the prohibited cattle materials in the product and the benefits of the product or how such restrictions are not necessary to ensure the safety of the product; and

(E) Any other relevant information.

(iii) FDA shall respond in writing to all requests for an exception or alternative to the requirements and may impose conditions in granting any request.

(3) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records.* (1) Establishments that manufacture an HCT/P that is manufactured using, or otherwise contains, cattle material must establish and maintain records sufficient to demonstrate that the material is not manufactured using, and does not contain, prohibited cattle materials.

(2) Records must be retained for the period specified in § 1271.270(d).

(3) Records must be retained at the manufacturer's establishment or at a reasonably accessible location. Records are considered to be reasonably accessible if they are accessible from an onsite location.

(4) Records required by this section must be available to FDA for inspection and copying. All the records must be in English.

(5) When filing entry with the U.S. Customs and Border Protection, the importer of record of an HCT/P manufactured using, or otherwise containing, cattle material must affirm that the HCT/P was manufactured using, or otherwise contains, cattle material and must affirm that the HCT/P was manufactured in accordance with this section. If an HCT/P was manufactured using, or otherwise contains, cattle material, then the importer of record must, if requested, provide to FDA within 5 days records that are sufficient to demonstrate that the HCT/P is not manufactured using, and does not contain, prohibited cattle material.

(d) An HCT/P that is not in compliance with the requirements of paragraph (b) or (c) of this section is a violative HCT/P that is subject to retention, recall, destruction, and/or cessation of manufacturing under § 1271.440.

Dated: December 7, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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