January 19, 2007

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

On January 12, 2007, the U.S. Food and Drug Administration ("FDA") proposed to prohibit the use of certain cattle material in the production and manufacture of medical products intended for human use and in drugs intended for use in ruminant animals.[1] In addition to banning the use of certain cattle material, the proposed regulation would require manufacturers to establish and maintain records documenting that the products meet the regulation's requirements. The proposal would also ban the extralabel use in ruminants[2] of products approved for use in other animals and produced or manufactured containing the restricted cattle material.[3] The proposed regulations are part of FDA's continuing efforts to reduce the risk of potential human exposure to bovine spongiform encephalopathy ("BSE") and related human disease. FDA published an interim final rule in 2005 that bans the use of similar cattle material in food, dietary supplements, and cosmetics.

Written or electronic comments should include the docket number 2005N-0373 and RIN number 0910-AF54. Comments regarding the proposed rule must be submitted to FDA by March 13, 2007. Comments regarding the proposal's information collection requirements must be submitted to FDA by February 12, 2007. Requests for an informal hearing on the proposed ban related to medical devices must be submitted to FDA by February 12, 2007.

A. Use of Cattle Material in Manufacturing Process

FDA's proposed rule would ban the use of "prohibited cattle material" in manufacturing or use in drugs,[4] biologics, and medical devices intended for use in humans, as well as in human cells, tissues, and cellular and tissue-based products ("HCT/Ps") (collectively, medical products for humans). The restriction would also extend to drugs intended for use in ruminant animals. The regulations would be promulgated at 21 C.F.R. §§ 300.200, 500.200, 600.16, 895.102, and 1271.470. The only notable difference in the proposed regulations for the various medical products covered by the proposal is the recordkeeping requirement, as discussed in more detail below. Failure to comply with the proposed regulations would render the medical product adulterated.[5]

[1] 72 Fed. Reg. 1582 (Jan. 12, 2007)

[2] A "ruminant" is "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." 72 Fed. Reg. 1582, 1614 (Jan. 12, 2007).

[3] Because all human drugs would be prohibited from using the excluded material, the principal impact of this rule would be on any animal drugs approved for non-ruminant species and containing the excluded material.

[4] The rule covers NDA-ANDA approved drugs, OTC monograph drugs, and homeopathic drugs.

[5] HCT/P that does not comply with the proposed regulations would be "subject to retention, recall, destruction, and/or cessation of manufacturing under 21 C.F.R. § 1271.440." 72 Fed. Reg. 1582, 1619.

B. Definitions

The proposed rule establishes or adopts the following definitions, which are repeated in each of the provisions covering each class of medical product:

Prohibited cattle materials: "specified risk materials, small intestine of all cattle [with limited exception][6], 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."

Inspected and passed: "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."

Mechanically separated: "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)."

Nonambulatory disabled cattle: "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."

Specified risk material (SRM): "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."

Tallow: "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 and 5 U.S.C. § 552(a) and 1 C.F.R. Part 51.

Tallow derivatives: "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."

[6] The proposed regulations would allow of the small intestine of cattle "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." See 72 Fed. Reg. 1582, 1612-13.

C. Exception or Alternative

Under the regulation, medical products for humans and drugs intended for ruminant animals may not contain or be manufactured using prohibited cattle materials. However, companies could seek written permission from FDA for an exception or alternative to the regulations' requirements. A company's written request must include five components, the first four of which are: (a) a statement of the reasons why an exception or alternative is needed; (b) a description of the product; (c) a description of the source of the prohibited cattle materials; and (d) any other relevant information. The fifth component for medical products for humans would be 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. The final requirement for drugs for ruminant animals would be 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. FDA must respond to all requests in writing and may impose additional conditions in granting a request for an exception or alternative.

D. Recordkeeping and Access Requirements

The proposed rule would require manufacturers of medical products for humans and drugs intended for ruminant animals to establish and maintain records sufficient to demonstrate that the product is not manufactured from, and does not contain, prohibited cattle materials. The regulation would require that the records are: (1) retained at the manufacturer's establishment or at a "reasonably accessible location";[7] (2) readily available to FDA for inspection and copying; and (3) maintained in English.

When filing entry documentation with the U.S. Customs and Border Protection, importers of medical products for humans and drugs intended for ruminant animals must affirm that the product does not contain, and was not manufactured from, prohibited cattle materials. The importer must file supporting documentation with FDA if requested.

The regulations impose different document retention requirements related to the use of prohibited cattle material on the various medical products. For human drugs, the records would 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.

Drugs intended for use in ruminant animals have different document retention schemes for Type A medicated articles and other products. Records for a Type A medicated article intended for use in ruminants that is manufactured from or otherwise contains any cattle material would be retained for at least 2 years after distribution by the manufacturer. Records for drugs intended for use in ruminants, other than a Type A medicated article, that are manufactured from or otherwise contains cattle material would be retained for at least 1 year after the expiration date of the drug.

[7] "Records are considered to be reasonably accessible if they are accessible from an onsite location." 72 Fed. Reg. 1613.

The proposed document retention regulations for biological products, medical devices and HCT/Ps would impose the general document retention regulations currently in effect for those products. For biological products, the documents "must be retained consistent with § 600.12(b)," which generally requires retention until the latest of either five years after the records of manufacture or six months after the last expiration date of the individual product. Manufacturers must maintain medical device records "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."[8] Lastly, manufacturers must maintain records relating to HCT/Ps for 10 years after creation or 10 years from the date of administration, distribution or expiration of the product, whichever is longer.[9]

E. Extralabel Drug Use in Animals

The proposed regulation would also ban the use of drugs that contain prohibited cattle material from extralabel use in ruminants.[10] Moreover, the regulation would require any approved new animal drug containing prohibited cattle material to bear the following statement: "Federal law prohibits the extralabel use of this product in ruminants."[11] Any product that fails to include the labeling statement would be deemed misbranded.

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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[8] 21 C.F.R. § 820.180(b).

[9] 21 C.F.R. § 1271.270(d).

[10] 72 Fed. Reg. 1582, 1615. As noted earlier, because all human drugs would be subject to the ban on using the prohibited cattle material, the impact would likely be on the veterinarian's ability to use animal drugs approved for use in non-ruminant species that were made or produced with the banned cattle material.

[11] FDA estimates that only 8 products would be subject to this requirement. 72 Fed. Reg. at 1605.