SUPPORTING STATEMENT

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

A. Justification

1. Circumstances of Information Collection

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, and in drugs intended for use in ruminant animals. 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 589.2000 having ingested material prohibited under ;
- 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.

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.

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 specified risk materials, (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.

2. Purpose and Use of Information

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. 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. 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. 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 Cruetzfeldt-Jakob disease 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.

3. Use of Improved Information Technology

The proposed regulation does not specifically prescribe the use of automated, electronic, mechanical, or other technological techniques or other forms of information technology as necessary for use by firms. Companies are free to use whatever forms of information technology may best assist them in their recordkeeping. Records on bovine materials and ingredients may be kept in paper or electronic form, as long as they are easily accessible by FDA should the need arise. Maintenance of electronic records is acceptable and electronic records are considered to be reasonably accessible if they are accessible from an onsite location.

4. Efforts to Identify Duplication

This information is not otherwise submitted to the agency, and thus, there is no duplicate reporting.

5. Involvement of Small Entities

As explained in the Analysis of Economic Impacts section of the proposed rule, the proposed rule is unlikely to have a significant impact on a substantial number of small entities.

6. Consequences If Information Collected Less Frequently

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. To provide consistent protection across the range of FDA-regulated products, it is necessary to put in place the measures as set forth in the proposal.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

None of the collection requirements are inconsistent with 5 CFR 1320.5(d)(2).

8. Consultation Outside the Agency

The public will have the opportunity to comment on the proposed rule. All comments will be summarized and responded to in the final rule.

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this provision.

10. Assurance of Confidentiality

Confidentiality is protected under 21 CFR part 21 as well as 21 CFR 314.430 for human drugs and similar provisions for other drugs and medical devices covered under this proposal.

11. Questions of a Sensitive Nature

This information collection does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Hour Burden

Reporting. As discussed in the Analysis of Impacts section of the proposed rule, 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 the tables below, 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.

Under proposed §§ 300.200(c)(5), 500.200(c)(5), 600.16(c)(5), 895.102(c)(5), and 1271.470(c)(5), importers 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. As discussed in the Analysis of Impacts section, 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 the tables below, that this proposed provision would take each importer of record approximately 2.5 hours annually to process.

Recordkeeping. 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. 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. 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. 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. 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. 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 the tables below, 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 section, we estimate that this recordkeeping burden will be about 1 to 3 hours per year. For purposes of this document, we estimate 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 the table below.

Table 1.--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)	3787	1	3787	2.5	9467.5
Total					9827.5

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

Table 2.--Estimated Annual Recordkeeping Burden[1]

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	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.

13. Estimates of Annualized Cost Burden to Respondents

As discussed in the Analysis of Impacts section of the proposed rule, 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.

As discussed in the Analysis of Impacts section of the proposed rule, 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.

As discussed in the Analysis of Impacts section of the proposed rule, the proposed 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. The table below shows the estimated recurring recordkeeping costs for this proposed rule.

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.

As discussed in the Analysis of Impacts section of the proposed rule, 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.

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.

Summary of Industry Costs for the Proposed Rule

As discussed in the Analysis of Impacts section of 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.

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.

14. Estimates of Annualized Cost Burden to the Government

FDA anticipates that any additional costs associated with the agency's review of the submissions under this proposal would be negligible.

15. Changes in Burden

This request for OMB approval is for a proposed rule.

16. Time Schedule, Publication, and Analysis Plans

No comprehensive tabulation of the data is planned or anticipated.

17. Displaying of OMB Expiration Date

The OMB expiration date will be announced in the final rule.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, A Certification for Paperwork Reduction Act Submission, of OMB Form 83-I.

PAPERWORK REDUCTION ACT SUBMISSION

Please read the instructions before completing this form. For additional forms or assistance in completing this form, contact your agency's Paperwork Clearance Officer. Send two copies of this form, the collection instrument to be reviewed, the supporting statement, and any additional documentation to: Office of Information and Regulatory Affairs, Office of Management and Budget, Docket Library, Room 10102, 725 17th Street NW, Washington, DC 20503.

1. Agency/Subagency originating request

FDA

2. OMB control number b. [ ] None

a. 0910 -

3. Type of information collection (*check one*)

a. [x] New Collection

b. [ ] Revision of a currently approved collection

c. [] Extension of a currently approved collection

d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired

e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired

f. [ ] Existing collection in use without an OMB control number

For b-f, note Item A2 of Supporting Statement instructions

4. Type of review requested (*check one*)

a. [x] Regular submission

b. [ ] Emergency - Approval requested by at close of comment period

c. [ ] Delegated

5. Small entities

Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No

6. Requested expiration date

a. [X] Three years from approval date b. [ ] Other Specify:____/__

7. Title – Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants – Proposed Rule

8. Agency form number(s) (*if applicable*)

9. Keywords 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.

10. Abstract Proposal 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, and in drugs intended for use in ruminant animals.

11. Affected public (*Mark primary with "P" and all others that apply with "x"*)

a. ___ Individuals or households d. ___ Farms

b. _x__ Business or other for-profit e. ___ Federal Government

c. ___ Not-for-profit institutions f. ___ State, Local or Tribal Government

12. Obligation to respond (*check one*)

a. [ ] Voluntary- (guidance document)

b. [x] Required to obtain or retain benefits

c. [Mandatory

13. Annual recordkeeping and reporting burden

a. Number of respondents – 3787_____

b. Total annual responses/records – 5068 _____

1. Percentage of these responses collected electronically – unknown

c. Total annual hours requested – 12383.50 _____

d. Current OMB inventory – none; This is a proposed rule___

e. Difference _____

f. Explanation of difference

1. Program change _____

2. Adjustment _____

14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)*

a. Total annualized capital/startup costs _____

b. Total annual costs (O&M) _____

c. Total annualized cost requested _____

d. Current OMB inventory _____

e. Difference _____

f. Explanation of difference This is a proposed rule___

1. Program change _____

2. Adjustment _____

15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*)

a. __ Application for benefits e.__ Program planning or management

b. __ Program evaluation f.__ Research

c. __ General purpose statistics g. x Regulatory or compliance

d. __ Audit

16. Frequency of recordkeeping or reporting *(check all that apply)*

a. [ ] Recordkeeping b. [ ] Third party disclosure

c. [x] Reporting

1. [x] On occasion 2. [ ] Weekly 3. [ ] Monthly

4. [ ] Quarterly 5. [ ] Semi-annually 6. [x] Annually

7. [ ] Biennially 8. [x] Other (describe) one-time___

17. Statistical methods

Does this information collection employ statistical methods

[ ] Yes [x] No

18. Agency Contact (person who can best answer questions regarding the content of this submission)

	Name: _____ Phone: _____

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