cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and 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 a 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 so many prescription drug manufacturers would be affected by the proposed rule, the agency believes that this rule could have a significant impact on a substantial number of small entities. Consequently, the agency does not certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. The following analysis, in conjunction with the preamble, constitutes the agency's initial regulatory flexibility analysis as required by the Regulatory Flexibility Act.

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 $127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The proposed rule would amend the current requirements for the content of human prescription drug labeling related to use in specific populations. The primary benefit of the proposed rule would be improved communication of clinically relevant information on the safe and effective use of prescription drugs by pregnant or lactating women. Although the agency is unable to quantify these benefits, this proposed rule is the product of over 10 years of consultation with stakeholders. Direct costs of the proposed rule are projected to range from approximately $0.8 million to $17.6 million in any single year, and over 10 years have a total present value of approximately $50.3 million with a 7-percent discount rate or $61.7 million with a 3-percent discount rate. The annualized costs over 10 years would be $7.2 million with both a 7-percent discount rate and with a 3-percent discount rate. Although the agency is unable to quantify the net benefits of this proposed rule, the rule responds to problems with existing labeling identified by current users of drug product labeling. FDA therefore concludes that the potential benefit of better informed health care providers and patients would justify the costs of the rule. Furthermore, the agency has determined that the proposed rule is not an economically significant rule as defined by the Executive order.

A. Need for the Proposed Rule

In response to concerns about the usefulness of the current "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug product labeling, FDA held a part 15 hearing and two advisory committee meetings and consulted with focus groups and the public to solicit comment on how to improve these subsections. During these discussions, participants said that current prescription drug product labeling lacks clarity and often fails to provide meaningful clinical information about drug exposure during pregnancy and lactation. Of equal concern, current prescription drug product labeling is not designed to address either inadvertent drug exposure in early pregnancy or the potential consequences of discontinuing during pregnancy a drug prescribed to the mother to treat a chronic condition. Moreover, the current system of pregnancy categories can be ambiguous, give a false impression of the comparative risks of different prescription drug products, and fail to adequately provide meaningful information that health care providers can use to advise their patients on the safe and effective use of prescription drugs during pregnancy.

This rule, therefore, proposes to improve the quality of prescription drug labeling. Providing up-to-date information on the safe and effective use of prescription drugs during pregnancy and lactation in a standardized format would make labeling a more reliable resource that health care providers could consult when they seek prescription drug information for their pregnant and lactating patients.

B. Scope of the Proposed Rule

This proposed rule would affect human prescription drugs that would be required to have labeling with a "Pregnancy" or "Lactation" subsection. Some manufacturers with multiple dosage forms, dosage strengths, and package sizes of the same active ingredients may produce a single version of the labeling to use with all products. Nevertheless, for this analysis, FDA assumes that manufacturers will produce separate labeling for each dosage form, but will use the same version for all package sizes and dosage strengths of the same dosage form. This assumption may lead to an overestimation of the costs of the proposed rule.

C. Costs of the Proposed Rule

The extent to which the proposed rule might affect labeling depends on whether an affected application is subject to the PLR. The labeling for applications subject to the PLR would need to conform to the proposed content requirements for the "Pregnancy" and "Lactation" subsections of the "Use in Specific Populations" section of the full prescribing information (proposed §§ 201.57(c)(9)(i)-(c)(9)(ii)). The labeling of applications not subject to the PLR would only need to conform to the proposed requirement to remove the pregnancy category if it exists. The level of effort required to comply with the proposed changes, therefore, would depend on whether the affected application is subject to the requirements of the PLR. In the analysis of costs, multiple applications for the same prescription drug product are counted only once.

1. Affected Applications

a. *Future applications.* NDAs, BLAs, and efficacy supplements submitted on or after the effective date of the pregnancy labeling final rule are future applications. Even though the number of future applications is unknown, for the analysis of impacts for the PLR (71 FR 3922 at 3969), FDA examined approvals from 1997 to 2001 to estimate the average annual number of applications that might be submitted in the future (i.e., after the effective date of the PLR). An updated analysis of the FDA approval data suggests that these estimates remain representative of current activity. Thus, FDA continues to

use the numbers derived for the PLR analysis as the agency's best estimate of future activity. Table 2 of this document shows that manufacturers might submit an estimated 1,580 applications in the 10 years following the effective date of the pregnancy labeling final rule, with approximately 75 percent of these submissions being for innovator products.

b. *Approved or pending applications subject to the PLR.* Any approved or pending application subject to the requirements of the PLR would also need to conform to the requirements of this proposed rule. This includes applications pending on the effective date of the pregnancy labeling final rule and those applications approved between June 30, 2001, and the effective date of the pregnancy labeling final rule. For the purposes of this analysis, FDA assumes that the pregnancy labeling final rule would become effective on June 30, 2010, and affect some applications counted as future applications in the PLR analysis.

This analysis uses FDA's approval data to tally the number of affected approvals between June 30, 2001, and June 30, 2006. This number provides a partial estimate of the number of approved or pending applications that might be affected by the proposed rule. Because the number of applications that would be submitted between June 30, 2006, and the effective date of the pregnancy labeling rule is unknown, FDA uses the estimate of the number of future applications in years 5 to 10 from the PLR analysis to complete the estimate of the number of approved or pending applications subject to the PLR that might be affected by this proposed rule.

To minimize the burden on industry, FDA proposes that manufacturers with labeling that already conforms to the PLR requirements on the effective date of the pregnancy labeling final rule would have from 3 to 5 years to revise labeling to conform to the requirements of the rule. Table 2 of this document shows that the existing labeling of an estimated 1,300 innovator applications and 600 generic applications would need to be revised to add the new content that would be required by the pregnancy labeling final rule.

TABLE 2.—ESTIMATED NUMBER OF APPLICATIONS SUBJECT TO THE PLR[1]

Year	Future Applications		Pending or Recently Approved Applications		Total	
	Innovator Drugs	Generic Drugs	Innovator Drugs	Generic Drugs	Innovator Drugs	Generic Drugs
1	140	40	0	0	140	40
2	130	40	0	0	130	40
3	120	40	380	260	500	300
4	120	40	480	130	600	170
5	120	40	440	210	560	250
6	110	40	0	0	110	40
7	110	40	0	0	110	40
8	110	40	0	0	110	40
9	110	40	0	0	110	40
10	110	40	0	0	110	40
Total	1,180	400	1,300	600	2,480	1,000

[1] Numbers include an estimated 1,613 pending or future applications (Source: See ANDAs, efficacy supplements, new NDAs and BLAs for years 5 to 10 of table 14 in 71 FR 3922 at 3977 through 3978), and 1,900 approved applications when the pregnancy labeling final rule becomes effective (Source: Analysis of approvals from June 29, 2001, to June 30, 2006, using FDA's approval data). Numbers may not sum due to rounding.

c. *Approved applications not subject to the PLR.* The proposed rule would require that manufacturers responsible for the labeling of approved applications not subject to the requirements of the PLR make minor revisions to remove the pregnancy category from the existing "Pregnancy" subsection of the "Precautions" section of the labeling. Manufacturers would have 3 years after the effective date of the pregnancy labeling final rule to make this change. This provision of the proposed rule would affect any approved application not subject to the PLR that currently has labeling that contains a pregnancy category. Although the actual number of applications that would be affected by this provision of the proposed rule is uncertain, the recent analysis of FDA's approval data suggests that the labeling of up to 4,720 existing prescription drug products could be affected in year 3 of the rule. Because the labeling of many older products initially approved before 1979 might not contain a pregnancy category, this estimate is an upper bound. Moreover, it should be noted that manufacturers sometimes voluntarily discontinue marketing older products and might do so before they would be required to remove the pregnancy category. Although the magnitude is uncertain, this natural attrition would likely reduce the number of products that would be affected by the pregnancy labeling final rule.

2. One-Time and Annual Labeling Costs

a. *One-time costs.* The actions required under this proposed rule to create drug product labeling can be divided into two major categories: (1) Collecting and organizing the additional information required by this proposed rule and (2) revising existing labeling to add or remove information. FDA notes that designing the labeling is a routine cost of a new application and would not be attributable to this proposed rule. To conform to the requirements of the proposed rule, manufacturers might spend more time on these actions than

they currently spend preparing the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the labeling, thus incurring additional labeling costs. Which costs would be incurred by a manufacturer will depend on when in the product's life cycle the labeling subject to the pregnancy labeling final rule would be required and whether the application is subject to the PLR. For example, manufacturers with future innovator applications would only incur costs to collect and organize the required information because designing labeling is a routine cost of a new application. In contrast, manufacturers required to change existing product labeling would incur both types of costs (i.e., collecting and organizing required information, and revising existing labeling).

i. *One-time costs to collect and organize the new content.* Manufacturers responsible for applications subject to the new content requirements would need to collect and organize the information required for the appropriate subsections of the "Use in Specific Populations" section of the labeling. Specifically, the proposed rule would merge the information in the "Pregnancy" and "Labor and delivery" subsections and revise the "Nursing mothers" subsection. The merged subsection would be called the "Pregnancy" subsection and would require the following: (1) Information about pregnancy exposure registries, (2) a general risk statement, (3) a fetal risk summary, (4) clinical considerations, and (5) a discussion of data. The proposed rule would rename the "Nursing mothers" subsection the "Lactation" subsection and require the following: (1) A risk summary, (2) clinical considerations, and (3) a discussion of data.

Under the current system, applicants and FDA review any existing animal and human data and determine the appropriate pregnancy category. Although the proposed rule would no longer require that a drug be assigned to a pregnancy category, preparing the new labeling content might require more time than manufacturers currently spend preparing this part of the product labeling. FDA personnel have worked with manufacturers on a case-by-case basis to update certain prescription drug labeling to include content similar to the content that would be required by the proposed rule. This experience suggests that for innovator products, a physician or other health care professional might spend up to 10 hours collecting the new information. In addition, regulatory affairs and legal personnel might spend up to 10 hours organizing the information and discussing the new content with FDA. At hourly wage costs of $100 for medical personnel and $50 for regulatory and legal personnel, manufacturers would incur about $1,500 in additional costs (10 hours x $100 per hour + 10 hours x $50 per hour). Because labeling of generic drug products duplicates the labeling of reference listed drugs, FDA anticipates that manufacturers of generic products would not incur these incremental costs.

Furthermore, under § 314.50(l)(1)(i), all manufacturers submitting new or revised prescription drug labeling must prepare an electronic version of the labeling for submission to the agency. Some manufacturers may incur incremental costs to prepare and transmit an electronic version that is consistent with the XML (Extensible Markup Language)-based Structured Product Labeling (SPL) standard. Because FDA has little information on the impact of this step, FDA requests detailed comment from industry on these costs.

ii. *One-time costs to revise existing prescription drug labeling.* The agency has previously estimated that the cost of revising prescription drug labeling varies with the size of the manufacturer (68 FR 6062 at 6074, February 6, 2003). Product labeling involves many departments in a manufacturer, including legal, drug safety, regulatory affairs, layout, and production personnel. Larger manufacturers with several administrative layers may require more time to change labeling than smaller manufacturers with fewer layers. In addition to labor costs, manufacturers incur material costs for each change to drug product labeling, including artwork and labeling scrap. If the rule were to require a labeling revision without allowing sufficient time to deplete existing inventories of labeling, manufacturers might also lose the value of labeling that they must throw away.

Using 2004 wages, table 3 of this document shows the estimated labor and material costs for generic drug manufacturers and three sizes of innovator manufacturers to revise labeling. Because the proposed implementation schedule would allow manufacturers with approved or pending applications subject to the PLR a minimum of 3 years to revise product labeling to conform to the requirements of the pregnancy final rule, manufacturers are not expected to incur any additional inventory costs beyond scrap. Material costs, therefore, include only the average cost of artwork and scrap.

TABLE 3.—LABELING REVISION COSTS BY SIZE AND TYPE OF MANUFACTURER

Type of manufacturer	Labor Cost ($)	Material Cost ($)	Total Cost ($)
Generic:	1,000	500	1,500
Innovator (estimated share of products):			
Small (5 percent)	1,000	500	1,500
Medium (5 percent)	1,500	1,420	2,920
Large (90 percent)	2,180	2,020	4,200

Source: 68 FR 6062 at 6074, updating for 2004 costs and excluding excess inventory loss from the material costs.

FDA's approval data suggests that large manufacturers with 1,000 or more employees produce about 90 percent of the affected innovator prescription drug products. Assuming a uniform distribution of the other 10 percent of innovator prescription drug products among small and medium-size manufacturers, manufacturers of innovator prescription drug products may incur a weighted average cost of about $4,000 per product to revise existing product labeling ((5 percent small innovator manufacturers x $1,500) + (5 percent medium-size innovator manufacturers x $2,920) + (90 percent large innovator manufacturers x $4,200)). Generic drug manufacturers may incur about $1,500 per product to revise labeling.

iii. *One-time cost to prepare artwork for prescription drug labeling other than trade labeling.* The PLR requires that trade labeling (labeling on or within the package from which the drug is to be dispensed) be printed in a minimum of 6-point type size and that labeling

disseminated in other contexts (nontrade labeling) be printed in a minimum of 8-point type size (§ 201.57(d)(6)). In the analysis of impacts for the PLR, FDA assumed that manufacturers would incur additional costs for nontrade labeling because the 8-point type size requirement would require that manufacturers revise nontrade labeling to accommodate the larger type size. FDA makes the same assumption for prescription drug labeling incorporating the new pregnancy and lactation content: that affected manufacturers would incur additional one-time costs to revise nontrade labeling to accommodate the new pregnancy and lactation content in the 8-point type size. The agency previously estimated it would cost manufacturers about $810 per product to revise and proofread the layout, and to prepare artwork (71 FR 3922 at 3981). Updating for current material and labor costs, on average, FDA estimates that, on average, manufacturers might spend $1,000 for each affected innovator product.

b. *Annual incremental costs to print longer labeling.* Longer labeling increases the cost of paper, ink, and other ongoing incremental printing costs. Some requirements of the proposed rule would increase the length of labeling. The incremental increase will depend on many factors, including the number of animal and human studies that have been conducted and their findings, the known risks of the drug, and whether a pregnancy registry exists. Based on the agency's experience with recent labeling changes incorporating content similar to that proposed in this rule, labeling conforming to both the PLR and the proposed requirements might increase by approximately 15 square inches in 6-point type size and 24 square inches in 8-point type size.[4] Although the estimate is based on a small number of labeling changes, FDA concludes it reasonably approximates the additional amount of paper that would be needed. Nevertheless, FDA requests comment from industry on these assumptions.

i. *Trade labeling.* Manufacturers must send trade labeling with all shipments of prescription drugs and with any samples distributed to health care providers. The PLR requires that trade labeling be printed in a minimum of 6-point type size. The proposed new content requirements would increase the size of trade labeling by an estimated 15-square inches. To conserve space, trade labeling is normally printed on both sides of the paper. The proposed new content, therefore, would add about 7.5-square inches of paper to the overall size of trade labeling. The agency previously estimated that manufacturers would spend about $0.0086 to produce 100-square inches of labeling (65 FR 81082 at 81107). Updating for inflation, FDA estimates that manufacturers might spend $0.01 for each additional 100-square inches of labeling they produce.

The agency has also previously estimated that, on average, manufacturers annually send up to 650,000 pieces of trade labeling with each innovator product and up to 370,000 pieces of trade labeling with each generic product. In addition, industry wide, a total of 90 million pieces of trade labeling are distributed with drug samples each year (71 FR 3922 at 3979). Because the new content provisions of this proposed rule would only add about 7.5-square inches to the overall size of trade labeling, the cost of labeling for an affected innovator product would increase by approximately $470 each year (650,000 pieces per product x $0.000096 per square inch x 7.5-square inches per piece). Generic drug manufacturers would incur annual incremental printing costs of about $280 for each generic product affected by the proposed rule (370,000 pieces per product x $0.000102 per square inch x 7.5-square inches per product).

FDA assumes that almost all samples are innovator products. Although it is unlikely that all samples would be affected by the proposed rule, the annual cost of longer trade labeling accompanying all samples of innovator products could equal about $65,000 (90 million samples x $0.000096 per square inch x 7.5-square inches per piece).

ii. *Nontrade labeling.* The PLR requires that any nontrade labeling be printed in a minimum of 8-point type size. For applications subject to the PLR, the new content requirements of the proposed rule would increase the size of the paper needed to print nontrade labeling by approximately 24 square inches. FDA assumes that only innovator products would incur these costs because almost all nontrade labeling is for innovator products. The agency previously estimated that manufacturers might distribute to health care providers and consumers an annual average of 730,000 pieces of labeling during the first 3 years of the life of an innovator product (71 FR 3922 at 3981). FDA assumes that this estimate is also a reasonable estimate of the number of pieces of labeling that would be distributed in the first 3 years after a product is relabeled under this rule. Thus, a manufacturer might spend up to $5,100 per innovator product to print labeling in 8-point type size.[5]

iii. *Physicians' Desk Reference (PDR) costs.* The new content requirements of this proposed rule would add about 0.2 page to labeling printed in the PDR and would cost manufacturers an additional $2,350 annually for each affected product.[6] FDA assumes that these costs would be incurred by the pharmaceutical industry as fees paid to the publisher of the PDR. The total cost for a manufacturer to print longer labeling in the PDR depends on how many years the labeling remains in the PDR. In the economic analysis of the PLR, FDA assumed that only 75 percent of the affected innovator products would have labeling published in the PDR (some smaller manufacturers do not publish labeling in the PDR) and would continue to include the labeling in the PDR in subsequent years (71 FR 3922 at 3976). FDA makes the same assumptions for this analysis.

3. Summary of Industry Compliance Costs for the Proposed Rule

a. *One-time costs for applications subject to the PLR.* Manufacturers with future innovator applications or those with innovator applications pending on the effective date of the pregnancy labeling rule would incur one-time costs to collect and organize the information required for prescription drug labeling

[4] This estimate is based on the agency's sample labeling in the appendix, experience with recent case-by-case labeling changes, and the results of a study on new approvals between January 1, 1997, and December 31, 2002. The net increase in the number of characters was tallied for each case and for the hypothetical samples in the appendix. Using the average increase in the number of characters and the proportion of drug products for each pregnancy category, we estimate that prescription drug labeling could increase by a weighted average of 3,200 characters. Labeling can accommodate approximately 200 characters per square inch in 6-point type size and about 130 characters per square inch in 8-point type size. Therefore, 3,200 additional characters would require about 15-square inches of paper in 6-point type size and 24-square inches of paper in 8-point type size.

[5] For the PLR, the agency estimated that manufacturers would print and distribute 775,000 pieces of labeling in 8-point type size in the first year of the life cycle of an innovator drug product and 710,000 pieces in years 2 and 3. Compared to the 6-point type size, about 59 percent more paper would be needed to print the new content in 8-point type size. Printing on one side of the paper, manufacturers would need about 24 square inches more paper to accommodate the new content. For this analysis, manufacturers would spend about $5,100 per product to print longer labeling ((775,000 + 710,000 + 710,000) x $0.000096 per sq inch x 24 sq inches = $5,083).

[6] There are approximately 15,850 characters on an average page of the PDR. The new content adds, on average, 3,200 more characters, requiring an additional 0.2 page. Using the lowest per page cost shown on the 2006 PDR rate card, manufacturers might spend up to $2,350 per product to add the new content ($11,730 per page x 0.2 page).

conforming to the rule, but would not incur one-time costs to revise existing labeling. As explained in section VIII.C.2.a.i of this document, FDA estimates that manufacturers would spend approximately $1,500 to collect and organize the information for the new pregnancy and lactation content. In contrast, manufacturers with future generic applications would incur no additional costs.

Manufacturers with applications approved on or after June 30, 2001, up to and including the effective date of the pregnancy labeling final rule, would incur costs to collect and organize the new content information and to revise existing prescription drug labeling. As described in section VIII.C.2.a.ii of this document, the estimated average cost to revise existing labeling equals $1,500 for generic drugs and $4,000 for innovator drugs. Moreover, manufacturers with innovator products might incur another $1,000 to prepare the artwork for labeling not accompanying the prescription drug product. Therefore, manufacturers might spend a total of $6,500 for existing innovator labeling ($1,500 to gather and organize information for the new content + $4,000 to revise trade labeling + $1,000 to prepare artwork for labeling not accompanying the prescription drug product) and a total of $1,500 for existing generic labeling.

Table 4 of this document shows that total one-time labeling costs would be $11.1 million and range from $0.2 million to $3.5 million in any single year. As shown in table 2 of this document, after 10 years, the labeling of approximately 2,480 innovator drug products and about 1,000 generic drug products would include the new pregnancy and lactation content.

TABLE 4.—ONE-TIME COSTS TO PREPARE NEW CONTENT AND REVISE EXISTING LABELING FOR APPLICATIONS SUBJECT TO THE PLR[1]

Year	One-Time Costs ($ million)		
	Innovators	Generic	Total
1	0.2	0.0	0.2
2	0.2	0.0	0.2
3	2.7	0.4	3.0
4	3.3	0.2	3.5
5	3.0	0.3	3.4
6	0.2	0.0	0.2
7	0.2	0.0	0.2
8	0.2	0.0	0.2
9	0.2	0.0	0.2
10	0.2	0.0	0.2
Total	10.2	0.9	11.1

[1] Costs may not sum due to rounding. See table 2 of this document for details on the number and distribution of affected products.

b. *Annual incremental printing costs for applications subject to the PLR.*

i. *Trade labeling.* As described in section VIII.C.2.b.i of this document, the agency estimates that each year manufacturers print an average of about 650,000 pieces of trade labeling for each innovator product and an average of about 370,000 pieces of trade labeling for each generic product. Based on the average number of pieces of trade labeling and the estimated number of affected applications subject to the PLR from table 2 of this document, table 5 of this document shows the cumulative number of pieces of trade labeling that would be affected by this proposed rule.

TABLE 5.—CUMULATIVE NUMBER OF PIECES OF PRESCRIPTION DRUG TRADE LABELING BY TYPE OF PRODUCT FOR APPLICATIONS SUBJECT TO THE PLR[1]

Year	Cumulative Number of Pieces (million)		
	Innovator	Generic	Samples
1	90	10	90
2	180	30	90
3	500	140	90
4	890	200	90
5	1,250	300	90
6	1,330	310	90
7	1,400	330	90
8	1,470	340	90
9	1,540	360	90
10	1,610	370	90

[1] Numbers may not sum due to rounding. The cumulative calculation assumes that manufacturers print 650,000 pieces for each innovator product and 370,000 pieces for each generic product, and once a product is approved, it remains on the market for the entire analysis.

Printing longer trade labeling would cost manufacturers a total of $9.9 million over 10 years, including $7.4 million for innovator trade labeling, $1.8 million for generic trade labeling, and $0.7 million for trade labeling accompanying samples. As shown in table 6 of this document, annual costs to print the additional information that would be required by this proposed rule range from $0.1 million in year 1 to $1.5 million in year 10. However, if at some point in the future, manufacturers can supply trade labeling electronically, the rule will cease to impose these annual incremental printing costs.

TABLE 6.—ANNUAL INCREMENTAL PRINTING COSTS FOR LONGER TRADE LABELING[1]

Year	Costs by Type[2] ($ million)			
	Innovator	Generic	Samples	Total
1	0.1	0.0	0.1	0.1
2	0.1	0.0	0.1	0.2
3	0.4	0.1	0.1	0.5
4	0.6	0.2	0.1	0.9
5	0.9	0.2	0.1	1.2
6	1.0	0.2	0.1	1.3
7	1.0	0.2	0.1	1.3
8	1.1	0.3	0.1	1.4
9	1.1	0.3	0.1	1.5
10	1.2	0.3	0.1	1.5
Total	7.4	1.8	0.7	9.9

[1] Costs may not sum due to rounding.
[2] Manufacturers would incur printing costs of about $72.37 for every 100,000 pieces of innovator trade labeling and about $76.58 for every 100,000 pieces of generic trade labeling. Trade labeling accompanying prescription drug samples would cost industry about $65,132 annually. See section IX.C.2.b.i of this document for details.

ii. *Nontrade labeling.* As discussed in section VIII.C.2.b.ii of this document, the new content requirements of the pregnancy labeling final rule likely would require manufacturers to print longer nontrade labeling in 8-point type size during the first 3 years after adding the new content to labeling. FDA assumes that only innovator products would incur these costs because almost all nontrade labeling is for innovator products. Thus, over 10 years, manufacturers of innovator products might spend up to $12.6 million ($5,100 per innovator product x 2,480 innovator products) to print labeling in 8-point type size.

iii. *Physicians' Desk Reference.* As discussed in section VIII.C.2.b.iii of this document, manufacturers of innovator products may pay an additional $2,350 annually to include longer prescription drug labeling in the PDR. Because FDA assumes that, after the first year, labeling would remain in the PDR for all subsequent years, PDR printing costs are cumulative. As illustrated in table 7 of this document, in 10 years industry might incur a cumulative total of $27.8 million to print longer labeling in the PDR.

TABLE 7.—CUMULATIVE NUMBER OF AFFECTED APPLICATIONS AND ANNUAL INCREMENTAL COST OF LONGER LABELING PRINTED IN THE PDR[1]

Year	Cumulative Number of Affected Innovator Applications[2]	Annual Incremental Cost ($ mil)
1	110	0.2
2	210	0.5
3	590	1.4
4	1,040	2.4
5	1,460	3.4
6	1,540	3.6
7	1,620	3.8
8	1,700	4.0
9	1,780	4.2
10	1,860	4.4

TABLE 7.—CUMULATIVE NUMBER OF AFFECTED APPLICATIONS AND ANNUAL INCREMENTAL COST OF LONGER LABELING PRINTED IN THE PDR[1]—Continued

Year	Cumulative Number of Affected Innovator Applications[2]	Annual Incremental Cost ($ mil)
Total Cost	27.8	

[1] Costs may not sum due to rounding.
[2] Seventy-five percent of innovator products adding new content (see table 2 of this document) would be included in the PDR.

c. *One-time costs for applications not subject to the PLR.* The proposed rule would require that manufacturers with approved prescription drugs not subject to the PLR remove the pregnancy category from labeling if a category exists. To minimize the impact on industry, the agency proposes to give manufacturers 3 years after the effective date of the pregnancy labeling final rule to make these changes. The proposed implementation schedule would give manufacturers sufficient time to deplete their stocks of labeling. Because removing the pregnancy category is a minor labeling change, manufacturers not subject to the PLR would only need to submit revised labeling with their annual reports. In most cases, the burden on manufacturers would be less than the average standard costs to revise existing labeling (see table 3 of this document). However, some manufacturers with multiple applications not subject to the PLR may need to revise simultaneously the labeling of many products, creating other costs than those estimated for standard labeling revisions. FDA requests detailed comment from industry about the potential burden of the implementation schedule for this provision of the proposed rule.

Based on an analysis of FDA's approval data, an estimated 4,720 prescription drug products would be affected by this provision of the proposed rule. The agency estimates that in year 3, manufacturers would remove the pregnancy category from labeling of 1,700 innovator prescription drug products and 3,020 generic prescription drug products, at a total cost of $11.3 million ((1,700 innovator products x $4,000 per innovator product) + (3,020 generic products x $1,500 per generic product)). This estimate likely overstates the direct compliance costs because many companies would remove the pregnancy category at the same time they voluntarily revise product labeling for other reasons.

d. *Summary of compliance costs.* The industry compliance costs of the proposed rule include the following: (1) One-time cost to prepare the new "Pregnancy" and "Lactation" subsections of trade labeling and labeling not accompanying prescription drug products, and (2) annual incremental costs to print longer labeling.

Similar to the rollout for PLR, FDA would provide training to medical reviewers on the requirements of the final pregnancy labeling rule. Nevertheless, reviewing the new labeling, including the longer content, would increase the review times and workloads of medical reviewers in the review divisions. Because the long-term impact of the rule depends on a number of uncertain factors, we are unable to quantify this burden on the agency.

As shown in table 8 of this document, the total present value of all costs equals $50.3 million with a 7-percent discount rate or $61.7 million with a 3-percent discount rate. The annualized cost would be $7.2 million with both a 7-percent discount rate and a 3-percent discount rate.

TABLE 8.—SUMMARY OF COMPLIANCE COSTS[1]

Year	One-time Costs ($ mil)	Annual Costs ($ mil)	Total Costs ($ mil)	Present Value ($ mil)	
				3%	7%
1	0.2	0.6	0.8	0.8	0.8
2	0.2	1.2	1.3	1.3	1.2
3	14.4	3.2	17.6	16.1	14.4
4	3.5	5.4	8.9	7.9	6.8
5	3.4	7.4	10.8	9.3	7.7
6	0.2	7.0	7.1	6.0	4.7
7	0.2	6.4	6.6	5.3	4.1
8	0.2	5.9	6.1	4.8	3.5
9	0.2	6.2	6.3	4.9	3.5
10	0.2	7.0	7.1	5.3	3.6
Total	22.5	50.3	72.7	61.7	50.3

[1] Costs may not sum due to rounding.

D. Benefits

This proposed rule is part of the agency's ongoing efforts to improve the quality of prescription drug labeling. To effectively communicate information about a drug, labeling should be easily accessible, understandable, accurate, reliable, and up-to-date. The agency's public health initiative to provide labeling in an electronic format is intended to make labeling accessible. This proposed rule would address the other aspects of effective communication and result in better quality prescription drug labeling. Once a prescription drug is approved, information starts to become available regarding clinical experience on the use of the drug during pregnancy or lactation. The purpose of this proposed rule is to ensure that prescription drug

labeling includes any available clinical information that can inform health care providers about the safe and effective use of prescription drugs during pregnancy and lactation. By requiring that manufacturers update prescription drug labeling with clinically relevant information, the proposed rule would improve the quality of labeling and could lead to better informed health care providers. The agency is unable to quantify the potential benefits of the proposed rule, but expects that better quality information in prescription drug labeling has the potential to improve the advice that health care providers give women about the safe and effective use of prescription drugs during pregnancy and lactation.

1. Current Use of Prescription Drugs.

a. *Women of reproductive age.* Many women between 15 and 44 years of age take prescription drugs. Data from the Medical Expenditure Panel Survey (MEPS) show that, in 2003, almost 70 percent of the women of reproductive age were prescribed at least one prescription drug (Ref. 32). Moreover, in a recent survey of medication use in adults, 82 percent of the women between 18 and 44 years of age reported using some type of medication in the week preceding the survey and 46 percent of these women reported using at least one prescription drug (Ref. 9).

b. *Pregnant women.* A recent retrospective study of over 150,000 pregnant women enrolled in 8 health maintenance organizations located throughout the United States found that within 270 days before delivery, over 60 percent of the women included in the study were dispensed a prescription drug other than a vitamin or mineral supplement (Ref. 33). Oral anti-infective drugs were the most commonly dispensed prescription drugs, accounting for about 40 percent of all dispensed drugs. Even though almost half of the pregnant women in this study received prescription drugs with pregnancy category A or B, over 30 percent received prescription drugs with pregnancy category C, and 2 percent received category D or X drugs (excluding female reproductive hormones). Similarly, a smaller study of rural obstetric patients in West Virginia found that, excluding prenatal vitamins and minerals, about 60 percent of the pregnant women in the study were prescribed a prescription drug (Ref. 34). Although this study did not examine the pregnancy category of the prescribed drugs, antibiotics were the most frequently prescribed type of drug.

These newer findings support findings reported in a 1994 Institute of Medicine report on women in clinical trials (Ref. 35). The report cited two studies from the 1980s on prescription drug use by pregnant women. One study found that pregnant women took an average of 3.8 medications and the other found that over 75 percent of pregnant women took 3 to 10 drugs during their pregnancy. Studies of pregnant women in several developed countries have found similar results for prescription drug use during pregnancy (Refs. 14, 36, and 37).

c. *Lactating women.* There is less information about the effect of prescription drugs on lactation than about effects on pregnancy. The percentage of new mothers who breast-feed their newborns continues to grow. A recent study found that the percent of mothers who breast-feed their newborns at some time increased from about 50 percent in 1990 to about 70 percent in 2003 (Ref. 38). With improved labeling, health care providers would have more concise clinical information about the use of prescription drugs during lactation, allowing women to make more informed choices about continuing to nurse their newborns while taking prescription drugs.

2. Current Pregnancy Labeling Is Not Adequate

Since 1979, most human prescription drug product labeling includes "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections. Besides providing information about a prescription drug's effect on reproduction, pregnancy, and the development of the fetus, each "Pregnancy" subsection must include a letter category (A, B, C, D, or X) intended to: (1) Communicate the prescription drug's reproductive and developmental risks or (2) weigh the risks and potential benefits of the prescription drug. The pregnancy letter category suggests increased risk as the letters ascend and equivalent risk for drugs with the same letter. This is a particular problem with category C because a prescription drug can be assigned this category when sponsors: (1) Lack both animal and human data or (2) have adverse animal data, but lack human data.

Pregnant women are rarely included in premarket clinical trials unless a drug is being developed to treat a condition unique to pregnancy. Consequently, few sponsors have any premarket data from pregnant women. Because human data on use during pregnancy are rarely available when a prescription drug is initially approved, category C is the most frequently assigned category. For example, a survey in the early 1990s found that about two-thirds of all prescription drugs in the hardcopy version of the PDR were in category C (Ref. 39). A recent search of the electronic PDR supports this observation. The study also found that over 60 percent of the prescription drugs with a pregnancy category were in category C (Ref. 40). Furthermore, once approved, prescription drugs tend to retain their initial pregnancy category.

Current labeling fails to provide up-to-date information about prescription drug use by pregnant or lactating women. Since the 1990s, the Teratology Society and health care providers have called for the agency to replace the current pregnancy categories with narrative statements that summarize and interpret all available human data.

3. Potential Benefits From Better Quality Labeling

As described in sections II and III of this document, FDA has consulted extensively with stakeholders interested in the use of prescription drugs during pregnancy and lactation. This proposed rule is in part a result of those consultations and would ensure that labeling contains clinically relevant information about prescription drug use during pregnancy and lactation to help health care providers and their patients make informed decisions about their treatment options. Although FDA has little information about adverse outcomes related to incomplete labeling information, better informed decisions about treatment options would likely lead to better outcomes.

a. *Treatment of chronic diseases during pregnancy or while lactating.* Improved information about the safe and effective use of prescription drugs during pregnancy would benefit health care providers and their patients who are pregnant and require medication to treat chronic diseases. The number of women who may benefit from better informed health care providers depends on many factors, including the prevalence of chronic diseases in pregnant women. Some chronic diseases (such as asthma, diabetes, hypertension, mental illness, and epilepsy) may result in negative health outcomes if left uncontrolled during pregnancy and lactation. Without adequate information, women with chronic medical conditions may receive suboptimal treatment, and suboptimal treatment may lead to poor health outcomes for the woman and her fetus. By requiring that manufacturers include human data, labeling will become a reliable source of up-to-date information on prescription drug use during pregnancy. Without complete

information about the benefits and risks of continuing medications during pregnancy, women with chronic medical conditions cannot make informed decisions about whether to stop taking their prescription drugs during pregnancy, and could take actions that might jeopardize their health or the health of their fetuses (Ref. 41).

i. *Pregnancy and asthma.* An estimated 6 million women of reproductive age have asthma. Previous studies have found that from 4 to 7 percent of pregnant women have asthma (Ref. 42); a recent study that used data from national health surveys conducted from 1997 to 2001 found that the annual prevalence of current asthma in pregnant women ranged from 3.7 to 8.4 percent (Ref. 43). Uncontrolled asthma has been associated with negative outcomes for both the pregnant women and the fetus.

ii. *Other chronic conditions.* The Centers for Disease Control and Prevention (CDC) tracks live births for women with several medical risk factors, including some chronic conditions requiring prescription drug therapy. For example, in 2003, of the approximately 4 million live births, some of the most frequent maternal risk factors included diabetes (3.3 percent), cardiac disease (0.5 percent), chronic (not pregnancy-related) hypertension (0.9 percent), and pregnancy-related hypertension (3.7 percent) (Ref. 44). Moreover, it has been reported that about 1 million women of reproductive age have epilepsy (Ref. 45) and up to 9 percent of pregnant women may experience depression (Ref. 46).

b. *Managing inadvertent exposure to drugs.* Improved information about the effects of inadvertent exposure to prescription drugs before women know they are pregnant would help health care providers to advise these women about the consequences of their inadvertent exposure. Because about one-half of the pregnancies in the United States are unintended, many women are taking prescription drugs before they are aware of the pregnancy (Ref. 41). Inadvertent exposure to prescription drugs during pregnancy may be of particular concern for women taking prescription drugs for chronic conditions. Fears about possible fetal harm from early exposure to prescription drugs can create anxiety for pregnant women and their families.

c. *Use of OTC drugs and dietary supplements by pregnant women.* Some studies in the United States have found that pregnant women often take over-the-counter (OTC) drugs and dietary supplements (Refs. 34, 47, and 48). It is possible that women are substituting these products for prescription drugs because OTC drugs and dietary supplements are perceived as being safer for use during pregnancy than prescription drugs. However, information on the safety of many of these products during pregnancy is as limited, if it is available at all, as that for prescription drugs. Furthermore, unlike prescription and OTC drugs, dietary supplements can be marketed without FDA premarket approval. Providing up-to-date information on the risks and benefits of prescription drugs may encourage more pregnant and lactating women to use safe and effective products that they might otherwise avoid.

4. Potential Benefits for Companies in the International Market

Besides the potential public health benefit of better informed health care providers, the proposed rule may benefit individual manufacturers operating on a global scale. In 1979, the United States began requiring that prescription drug manufacturers include a pregnancy category in the labeling of any systemically absorbed prescription drug. Although many European countries adopted similar category systems, recent guidance from the European Medicines Agency (EMEA) requires that prescription drug labeling include a narrative risk statement rather than a pregnancy category (Ref. 49). FDA's proposed rule would require narrative risk statements similar to those required by the EMEA. More consistent labeling at an international level may create some efficiency gains for global manufacturers marketing prescription drugs in both the United States and the European Union. FDA does not attempt to quantify these potential gains in efficiency.

E. Impacts on Small Entities

1. The Need for, and the Objectives of, the Proposed Rule

The current labeling for pregnant and lactating women provides limited clinical information for health care providers and their patients. The use of pregnancy categories is confusing and can be misinterpreted. The primary objective of the proposed rule is to modernize the content of the "Pregnancy," "Labor and delivery," and "Lactation" subsections of prescription drug product labeling and replace the category system with a narrative summary of potential risk. Narrative information can provide a valuable resource to clinicians and their patients about the relative risks and benefits of prescription drug use during pregnancy and lactation.

2. Description and Estimate of the Number of Small Entities Affected

This proposed rule would affect all small entities with applications required to include "Pregnancy" and "Lactation" subsections in the labeling. The Small Business Administration (SBA) considers Pharmaceutical Preparation Manufacturing firms (NAICS (North American Industry Classification System) 325412) with fewer than 750 employees and Biological Product Manufacturing firms (NAICS 325414) with fewer than 500 employees to be small entities. The U.S. Census Bureau reports that in 2002 there were 296 biological product manufacturing establishments (Ref. 50) and 901 pharmaceutical preparation manufacturing establishments (Ref. 51). However, Census employment size classes for pharmaceutical preparation manufacturing do not correspond to SBA size categories. For this analysis, any pharmaceutical preparation manufacturing establishment with less than 1,000 employees would be considered a small entity. Census data suggest that approximately 96 percent of biological product manufacturing establishments and no more than 97 percent of the pharmaceutical preparation manufacturing establishments could be considered small entities. Despite the large number of small entities, large companies manufacture most prescription drug products.

Because the labeling of all prescription drugs required to have a pregnancy category would be affected by the pregnancy labeling final rule, the agency expects this rule to have an impact on a substantial number of small entities. An analysis of FDA's approval data shows that about 60 small or privately held entities would be required to revise existing prescription drug labeling to conform to the content requirements between year 3 and year 5 of the proposed rule. An additional 180 small or privately held entities would be required to remove the pregnancy category from existing prescription drug labeling within 3 years of the effective date of the pregnancy labeling final rule, and many of these small entities would be required to remove the pregnancy category from more than 10 existing products. Because some of these entities would be required to make several labeling changes in the same year, the agency requests detailed comment from affected small entities on the potential burden of the proposed rule.

The compliance requirements for small entities under this proposed rule are the same as those described above for other affected entities. Compliance primarily involves revising subsections of prescription drug labeling to conform to the requirements of the proposed rule. Because manufacturers already submit labeling to FDA, no additional skills would be required to comply with the proposed rule. The small entities likely to bear the highest total costs under this proposed rule are those entities that would need to simultaneously revise the prescription drug labeling of several high-volume products. Because these small entities would likely have the highest sales volumes of affected products manufactured by small entities, the incremental cost per unit sold is likely to be relatively low. In contrast, small entities with a single, low-volume product would have a higher incremental cost per unit sold. The following examples illustrate possible impacts on small entities with different production volumes. Prescription drug labeling costs are estimated for a small entity that must revise labeling of an innovator product. Table 9 of this document outlines the projected per-unit and total costs to the entity with three different levels of production: 1,000, 10,000, and 100,000 units produced per year.

TABLE 9.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL ENTITY WITH A SINGLE INNOVATOR PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION[1]

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
One-Time Costs:[2]			
Add new content to existing trade labeling	$5,420	$5,420	$5,420
Prepare labeling not accompanying prescription drug products	$5,100	$5,100	$5,100
Total One-Time Costs	$10,520	$10,520	$10,520
Annual Incremental Costs:			
Printing longer trade labeling[3]	$80	$8	$1
Printing longer PDR[4]	$2,350	$2,350	N/A
Total Annual Incremental Costs	$2,430	$2,358	$1
Annualized Costs:[5]			
Total Annualized Costs at 3 percent	$3,660	$3,590	$1,230
Additional annualized cost per unit sold at 3 percent	$0.04	$0.36	$1.23
Total Annualized Costs at 7 percent	$3,920	$3,850	$1,500
Additional annualized cost per unit sold at 7 percent	$0.04	$0.39	$1.50

[1] Numbers may not sum due to rounding.
[2] Includes one-time costs to collect and organize information for the new content ($1,500), revise trade labeling ($2,920; see Medium firm in table 6 of this document), prepare artwork for labeling in 8-point type size ($1,000), and print labeling in 8-point type size to distribute directly to health care providers.
[3] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.0005 per piece.
[4] Assumes that products with less than 10,000 units per year will not have labeling in the PDR.
[5] One-time costs are annualized over 10 years.

Although this is an illustrative example, because the scope of the proposed rule would likely include most small entities, FDA uses the example of 100,000 units annualized over 10 years at a 7-percent discount rate to estimate the compliance costs as a proportion of average annual revenue. FDA calculated the average annual value of shipments for each employment category from data from the 2002 Economic Census. Because the agency's analysis of FDA's approval data found that at least one small entity might be required to revise the content of labeling for five innovator products in a single year, tables 10 and 11 of this document show the potential lower and upper bound impact on small manufacturing entities. Even with five affected products in a single year, annualized compliance costs would be less than 1.1 percent of average annual shipments for all establishment sizes.

TABLE 10.—ANNUALIZED COMPLIANCE COSTS AS A PERCENTAGE OF THE VALUE OF AVERAGE ANNUAL SHIPMENTS FOR SMALL PHARMACEUTICAL PREPARATION MANUFACTURING ESTABLISHMENTS (NAICS 325412)

Number of Employees	Number of Establishments	Annual Value of Shipments ($ mil)	Average Per Establishment Annual Value of Shipments ($ mil)	Hypothetical Annualized Costs as a Percentage of Average Annual Value of Shipments[1]	
				1 Affected Product	5 Affected Products
1-19	436	1,101.9	2.5	0.2%	0.8%
20-49	109	978.5	9.0	0.0%	0.2%
50-99	93	2,804.7	30.2	0.0%	0.1%

TABLE 10.—ANNUALIZED COMPLIANCE COSTS AS A PERCENTAGE OF THE VALUE OF AVERAGE ANNUAL SHIPMENTS FOR SMALL PHARMACEUTICAL PREPARATION MANUFACTURING ESTABLISHMENTS (NAICS 325412)—Continued

Number of Employees	Number of Establishments	Annual Value of Shipments ($ mil)	Average Per Establishment Annual Value of Shipments ($ mil)	Hypothetical Annualized Costs as a Percentage of Average Annual Value of Shipments[1]	
				1 Affected Product	5 Affected Products
100-499	184	23,773.2	129.2	0.0%	0.0%
500-999	48	35,262.7	734.6	0.0%	0.0%

Source: Table 4 in Ref. 50.
[1] One time compliance costs annualized at 7 percent for 10 years. Total annualized costs for this example total $3,920 per affected innovator product.

In the year that a small entity revises innovator labeling, the entity might spend up to $13,000 on one-time design costs, one-time printing costs for longer labeling in 8-point type size, and the annual incremental costs of printing longer trade labeling and a PDR listing conforming to the new content requirements. With five affected innovator products in a single year, compliance costs could total up to $65,000. However, FDA approval data suggest that it is unlikely that entities in the smallest category of establishments (i.e., less than 20 employees) would have 5 innovator products requiring revision in a single year. Nevertheless, $65,000 in compliance costs would total less than 4 percent of average annual revenues for an entity with less than 20 employees and less than 1 percent of average annual revenues for small entities with 20 or more employees.

TABLE 11.—ANNUALIZED COMPLIANCE COSTS AS A PERCENTAGE OF THE VALUE OF AVERAGE ANNUAL SHIPMENTS FOR SMALL BIOLOGICAL PRODUCT MANUFACTURING ESTABLISHMENTS (NAICS 325414)

Number of Employees	Number of Establishments	Annual Value of Shipments ($ mil)	Average Per Establishment Annual Value of Shipments ($ mil)	Hypothetical Annualized Costs as a Percentage of Average Annual Value of Shipments[1]	
				1 Affected Product	5 Affected Products
1-19	166	302.4	1.8	0.2%	1.1%
20-49	58	378.5	6.5	0.1%	0.3%
50-99	26	366.5	14.1	0.0%	0.1%
100-499	35	2,719.7	77.7	0.0%	0.0%

Source: Table 4 in Ref. 49.
[1] One time compliance costs annualized at 7 percent for 10 years. Total annualized costs for this example total $3,920 per affected innovator product.

F. Alternatives Considered

1. No New Regulatory Action

This alternative is the baseline against which FDA measures the costs and benefits of the other regulatory alternatives. The current "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the labeling, including the pregnancy categories, fail to provide relevant clinical information to health care providers and their patients about the safe and effective use of drug products during pregnancy and lactation. Current labeling also provides no information about the effects of inadvertent exposure before a woman knows she is pregnant.

2. Require the Labeling of Applications Submitted After the Effective Date of the Pregnancy Labeling Final Rule To Conform to the New Content Requirements; Remove the Pregnancy Category From the Labeling of All Other Approved Products ("Prospective Alternative")

This alternative would require that the new content be added only to the labeling for applications submitted after the effective date of the pregnancy final labeling rule. The scope of this alternative would be narrower than that of the proposed rule. Consequently, FDA estimates that 10 years after the effective date, 1,200 innovator products and 400 generic products would contain the new content. The estimated costs, therefore, would be less than those of the proposed rule. Because the labeling of fewer products would include the new pregnancy labeling content, the potential benefits of this alternative, although uncertain, might be less than those of the proposed rule.

This alternative would also require that, within 3 years of the effective date, manufacturers remove the pregnancy category (if it exists) from all labeling for products approved before the effective date of the pregnancy labeling final rule. FDA's approval data suggests that this requirement would affect about 2,990 innovator products and 3,630 generic products. Like the proposed rule, these changes to labeling would not require a separate labeling supplement, but would be submitted in an annual report.

FDA assumes that most cost components for this alternative are the same as for the proposed rule (see section VIII.C.2 of this document for details). However, because this alternative would only require new content prospectively, FDA anticipates

that no additional agency resources would be needed.

Table 12 of this document shows the estimated costs of this alternative. The estimated one-time costs to add the new content and remove the pregnancy category are $19.2 million. The annual incremental costs to print longer labeling that contains the new content are estimated at $22.3 million. The present value of the total compliance costs of this option would be approximately $29.9 million with a 7-percent discount rate or about $35.8 million with a 3-percent discount rate. The estimated annualized compliance costs for this alternative are $4.2 million with a 3-percent discount rate and $4.3 million with a 7-percent discount rate. Moreover, any overlap of the implementation schedules of the PLR and the pregnancy labeling final rule would reduce these costs because firms could make all labeling changes at the same time. However, any potential cost savings depend on the effective date of the pregnancy labeling final rule.

TABLE 12.—ESTIMATED COSTS OF THE PROSPECTIVE ALTERNATIVE

Year	One-Time Revision Cost ($ mil)	Annual Printing Costs ($ mil)	Total Costs ($ mil)	Present Value ($ mil)	
				3%	7%
1	0.2	0.6	0.8	0.8	0.8
2	0.2	1.2	1.3	1.3	1.2
3	17.6	1.6	19.2	17.6	15.7
4	0.2	1.9	2.1	1.8	1.6
5	0.2	2.1	2.3	2.0	1.7
6	0.2	2.4	2.5	2.1	1.7
7	0.2	2.6	2.8	2.3	1.7
8	0.2	2.9	3.0	2.4	1.8
9	0.2	3.1	3.3	2.5	1.8
10	0.2	3.9	4.1	3.0	2.1
Total	19.2	22.3	41.5	35.8	29.9

3. Require the Labeling of Categories of Drugs That Are Most Widely Used by Pregnant Women and Women of Reproductive Age To Conform to the Content Requirements

The scope of this alternative would be greater than that of the proposed rule. In the agency's efforts to develop this proposed rule, it consulted with outside experts concerning what drugs should be covered by this rule. FDA asked the American College of Obstetrics and Gynecology, the American Academy of Pediatrics, and the Association of Women's Health, Obstetric and Neonatal Nurses were asked about which drugs each thought were important to the clinical care of pregnant women and for which drugs more information is needed. FDA asked the Organization of Teratology Information Services and Motherisk, two organizations that counsel pregnant women about exposure to drugs during pregnancy, to list the drugs about which they received the most questions from pregnant women. FDA also consulted the March of Dimes and the Canadian Pediatric Society. In addition, FDA asked the Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs to consider how to determine which drugs merited priority implementation of the new content and format for pregnancy labeling. Consultation with these experts resulted in numerous lists of drugs for which revised pregnancy labeling was considered a priority. However, no clear core set of drugs or drug classes emerged from this process. The agency compiled a list of drug classes from those suggested by the various sources. The list included analgesics, anti-infective drugs, anticoagulants, antidepressants, antiemetics, anticonvulsants, antifungals, antihypertensives, antimigraine drugs, antivirals, respiratory agents, thyroid drugs, tranquilizers, oral contraceptives, glucocorticoids, estrogens, gastrointestinal drugs, and antihistamines. Changing the content and format of pregnancy labeling for such a large universe of drugs would be a large burden for both industry and FDA. Because of the difficulties of identifying the products affected by this alternative, FDA did not estimate the costs of this alternative, but expects that they would fall somewhere between those of the proposed rule and the highest cost alternative described below.

4. Require the Labeling of All Approved Products To Conform to the New Content Requirements

In contrast to the proposed rule, this alternative has the broadest scope and would require that new content be added to the labeling of about 4,170 innovator products and 4,030 generic products. Consequently the estimated costs and potential benefits would be greatest with this alternative.

The implementation schedule and estimated costs for future applications and for approved applications subject to the PLR would be the same as for the proposed rule. Approved applications not subject to the PLR would follow a staggered implementation schedule in which manufacturers would be given from 6 to 10 years to revise product labeling, depending on the approval date. Under this staggered schedule, manufacturers with applications approved before June 30, 1975, would have 6 years to revise labeling; manufacturers with applications approved between June 30, 1975, and June 29, 1984, would have 7 years to revise labeling; manufacturers with

applications approved between June 30, 1984, and June 29, 1990, would have 8 years to revise labeling; manufacturers with applications approved between June 30, 1990, and June 29, 1996, would have 9 years to revise labeling; and manufacturers with applications approved between June 30, 1996, to June 29, 2001, would have 10 years to revise labeling.

The length of time since a product's approval determines the amount of information available for the new content. In general, more information about clinical experience is available for older products than for newly approved products. Thus, FDA expects that manufacturers with applications not subject to the PLR might spend more time collecting and organizing the new content and that the costs to print longer labeling may exceed those estimated for applications subject to the PLR. Because the new content for older products could be longer than that for newly approved products, additional FDA personnel might be needed to review the labeling supplements for older products.

To account for these potential differences in the costs for the labeling of older products, this analysis uses a range of costs for products not subject to the PLR. One-time costs to collect and organize information range from $3,000 to $6,000 for innovator products. The length of trade labeling might increase by 12-square inches at a cost of $750 for innovator products and $450 for generic products. If the labeling of older products is longer than that of newly approved products, manufacturers with older innovator products might incur costs for labeling distributed directly to consumers and health care providers and costs to print longer labeling in the PDR. For this alternative, FDA estimates that, on average, labeling printed in 8-point type size would increase by 38 square inches at a cost of $8,050, and the PDR would be about 0.3 page longer at a cost of $3,950. Finally, to account for a potential increase in FDA resources for this alternative, the number of additional FTEs would double from two to four for the last 5 years of the analysis.

Over 10 years, the one-time costs to revise labeling to add the new content could range from $29.2 million to $34.3 million. Annual incremental printing costs might total about $91.5 million over 10 years. The present value of the total compliance costs range from about $75.3 million to about $78.2 million with a 7-percent discount rate and from about 97.9 million to about $101.9 million with a 3-percent discount rate. The estimated annualized compliance costs for this alternative, therefore, range from $11.5 million to $11.9 million with a 3-percent discount rate and range from $10.7 million to $11.1 million with a 7-percent discount rate. Table 13 shows the upper bound estimate for this alternative.

TABLE 13.—UPPER BOUND ESTIMATED COSTS OF HIGHEST IMPACT ALTERNATIVE

Year	Number of Approved Applications by Type of Product		Total Costs ($ mil)	Present Value ($ mil)	
	Innovator	Generic		3%	7%
1	140	40	1.3	1.2	1.2
2	130	40	1.8	1.7	1.5
3	500	300	6.7	6.1	5.5
4	600	170	9.3	8.3	7.1
5	560	250	11.2	9.7	8.0
6	480	630	15.5	13.0	10.3
7	430	720	16.7	13.6	10.4
8	390	650	17.7	13.9	10.3
9	450	670	20.0	15.3	10.9
10	490	560	25.6	19.1	13.0
Total	4,170	4,030	125.8	101.9	78.2

5. Summary of Regulatory Options

Table 14 of this document shows the total and incremental costs of the proposed rule and regulatory alternatives. The total benefits of the regulatory alternatives would be directly related to the costs, because the more costly the alternative the more products that would be covered. It should be noted that although the total benefits would correspond to the total costs, the marginal benefits of these alternatives may not correspond directly to marginal costs. FDA is unable, however, to quantify the total or incremental benefits of these regulatory alternatives.

The requirements of this proposed rule are the result of the agency's efforts to revise the regulations concerning the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug labeling. Although the prospective alternative has lower costs than the proposed rule, it would result in two types of PLR labeling—one with the revised pregnancy and lactation content and one without the revised content. To ensure the consistent quality of labeling subject to the PLR, the agency, therefore, proposes that the pregnancy labeling rule apply to all labeling subject to the PLR.

TABLE 14.—COMPARISON OF THE ESTIMATED COMPLIANCE COSTS OF THE PROPOSED RULE AND THE REGULATORY ALTERNATIVES[1]

Alternatives	Annualized costs ($ million)		Incremental costs ($ million)	
	3 percent	7 percent	3 percent	7 percent
No new regulatory action	0	0	N/A	N/A
Content required for labeling prospectively	4.2	4.3	4.2	4.3
Proposed rule	7.7	7.6	3.5	3.3
Content required for labeling of most widely used drugs	7.7 < x < 11.9	7.6 < x < 11.1	0 < x < 4.2	0 < x < 3.5
Content required for labeling of all approved drugs	11.5 to 11.9	10.7 to 11.1	3.8 to 4.2	3.1 to 3.5

[1] The present value of the total estimated compliance costs are annualized over 10 years at a 3–percent discount rate or a 7–percent discount rate. Compliance costs include the costs to remove the pregnancy categories from labeling not subject to the content requirements of each alternative.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501 3520). A description of these requirements is given below, along with an estimate of the annual reporting 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 the collection of information.

FDA invites comments on: (1) Whether the 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: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

Description: The proposed rule would amend FDA regulations concerning the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drugs. The proposal would require that labeling include a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling would also include relevant clinical information to help health care professionals make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X. The "Labor and delivery" subsection would be eliminated because information on labor and delivery would be included in the "Pregnancy" subsection. The proposed rule is intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that will be useful for decisionmaking by women of childbearing age and their health care providers.

Under proposed §§ 201.57(c)(9)(i) and 201.57(c)(9)(ii), holders of approved applications[7] would be required to provide new labeling content in a new format—that is, to completely rewrite the pregnancy and lactation portions of each drug's labeling. These application holders would be required to submit supplements requiring prior approval by FDA before distribution of the new labeling, as required in § 314.70(b) or § 601.12(f)(1).

Under proposed § 201.80(f)(6)(i), holders of approved applications would be required to remove the pregnancy category designation (e.g., "Pregnancy Category C") from the "Pregnancy" subsection of the "Precautions" section of the labeling. These application holders would report the labeling change in their annual reports, as required in § 314.70(d) or § 601.12(f)(3).

The new content and format requirements of the proposed rule would apply to all applications that are required to comply with the PLR, including: (1) Applications submitted on or after the date the proposed rule becomes final; (2) applications pending on the date the proposed rule becomes final; and (3) applications approved from June 30, 2001, to the effective date of the pregnancy labeling rule.

Information collection subject to the PRA would consist of the following submissions under the proposed rule:

(1) Applications submitted on or after the effective date of the proposed rule (§§ 314.50; 314.70(b); 601.2; 601.12(f)(1));

(2) Amendments to applications pending on the effective date of the final rule (§ 314.60);

(3) Supplements to applications approved from June 30, 2001, to the effective date of the final rule (§ 314.70(b); 601.12(f)(1));

(4) Holders of applications approved before June 29, 2001, that contain a pregnancy category would be required to remove the pregnancy category designation by 3 years after the effective date of the final rule and include this labeling change in their annual report (§ 314.70(d), 601.12(f)(3)).

The information collection requirements and burden estimates are summarized in table 12 of this document. Based on data provided in section VIII of this document, FDA estimates that approximately 1,613[8] applications containing labeling consistent with this rulemaking would be submitted to FDA by approximately 885 applicants. Based on data provided in section VIII of this document, FDA estimates that it would take applicants approximately 20 hours to prepare and submit labeling consistent with this rulemaking. The estimate of 20 hours is

[7] As discussed previously, the term "application" refers to NDAs, BLAs, and efficacy supplements.

[8] 1,613 includes approximately 1,197 innovator and 416 generic drug products.

incremental, in that it applies only to the requirements for this rulemaking and does not indicate the total hours required to prepare and submit complete labeling for these applications. The information collection burden to prepare and submit labeling in accordance with §§ 201.56, 201.57, and 201.80 is approved by OMB under Control Number 0910–0572.

FDA also estimates that approximately 111 amendments to applications pending on the effective date of the pregnancy labeling final rule would be submitted to FDA as a result of this proposal, by approximately 81 applicants, and that it would take those applicants approximately 20 hours (incremental) to prepare and submit each amendment.

In addition, FDA estimates that approximately 1,789 supplements to approved applications would be submitted to FDA to update labeling in accordance with this proposal, that approximately 210 application holders would submit these supplements, and that it would take those application holders approximately 85 hours[9] (incremental) to prepare and submit each supplement.

FDA also estimates that approximately 4,720[10] annual reports containing labeling changes resulting from this rulemaking would be submitted to FDA by approximately 300 application holders, and that it would take application holders approximately 50 hours[11] to prepare and submit each revision.

FDA must request an extension of approval of this information collection every 3 years. For purposes of OMB approval for the first 3-year period, FDA divided the total hours in table 15 of this document (422,545 hours) by 3 to provide OMB an annualized estimate of burdens associated with this rulemaking (i.e., 140,848 hours).

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

Burden Estimate: Table 15 of this document provides an estimate of the annual reporting burden for the proposed pregnancy and lactation labeling requirements. FDA specifically requests comments on these estimates.

TABLE 15.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Category (21 CFR section)	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
New NDAs/ANDAs/BLAs/efficacy supplements submitted on or after effective date (§§ 314.50; 314.70(b); 601.2; 601.12(f)(1))	885	1.82	1,613	20	32,260
Amendments to applications pending on effective date (§ 314.60)	81	1.37	111	20	2,220
Supplements to applications approved 6/30/01 to effective date (§ 314.70(b); 601.12(f)(1))	210	8.52	1,789	85	152,065
Annual report submission of revised labeling for applications approved before 6/29/01 that contain a pregnancy category (§ 314.70(d); 601.12(f)(3))	300	15.73	4,720	50	236,000
Total					422,545

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

In compliance with section 3507(d) of the PRA, the agency has submitted the information collection requirements of this proposed rule to OMB for review. The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by June 30, 2008, to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–6974, or e-mailed to: *baguilar@omb.eop.gov*.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." In this proposed rule, FDA is proposing to revise its existing requirements concerning the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of labeling for human prescription drug and biological products. To the extent that a State requires labeling that conflicts with these requirements, the State required labeling would be subject to implied conflict preemption.

As stated in the preamble, this proposed rule would amend portions of FDA's regulations that were recently revised by the PLR. When FDA finalized

[9] The estimate for innovator companies is approximately 85 hours, and the estimate for generic companies is approximately 22 hours. For purposes of this information collection analysis, FDA used the higher estimate and invites comment on the time needed to prepare and submit these supplements.

[10] 4,720 includes approximately 1,697 innovator and 3,023 generic drug products.

[11] The estimate for innovator companies is approximately 50 hours, and the estimate for generic companies is approximately 22 hours. For purposes of this information collection analysis, FDA used the higher estimate and invites comment on the time needed to prepare and submit these supplements.

the PLR, the agency responded to comments regarding the product liability implications of revising the labeling for prescription drugs. Several comments on the proposed PLR had raised concerns about State requirements on drug labeling, often as a result of product liability lawsuits, that conflict with federal requirements. As a result of those comments, and in discussing federalism issues, FDA restated its longstanding views on preemption. For further discussion of this issue, see 71 FR 3922 at 3933 through 3936 and 3967 through 3969. FDA's statements in this regard are applicable to this proposed rule as well, and reflect the agency's current position on this issue. Section 4(c) of Executive Order 13132 instructs us to restrict any Federal preemption of State law to the "minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated." This proposed rule meets the preceding requirement because as discussed above, it would preempt State laws that conflict with these Federal requirements. Section 4(d) of Executive Order 13132 states that when an agency foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility, the agency "shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict." In this case, FDA foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility. Section 4(e) of Executive Order 13132 adds that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency "shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings."

FDA is seeking input from all stakeholders on the proposed requirements for the content and format of pregnancy labeling through publication of the proposed rule in the **Federal Register** and will consult with State and local officials in an effort to avoid conflict between State law and federal protected interests.

XI. Request for Comments

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

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA only through FDMS at *http://www.regulations.gov.*

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 addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

§ 201.56 [Amended]

2. Amend § 201.56 in paragraph (d)(1) by removing from the list of headings and subheadings the subheadings "8.2 Labor and delivery" and "8.3 Nursing mothers" and adding in their place the subheading "8.2 Lactation".

3. Section 201.57 is amended by removing and reserving paragraph (c)(9)(iii) and by revising paragraphs (c)(9)(i) and (c)(9)(ii) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

* * * * *

(c) * * *

(9) * * *

(i) *8.1 Pregnancy.* This subsection of the labeling must contain the following information in the following order:

(A) *Pregnancy exposure registry.* If there is a pregnancy exposure registry for the drug, the telephone number or other information needed to enroll in the registry or to obtain information about the registry must be stated at the beginning of the "Pregnancy" subsection of the labeling.

(B) *General statement about background risk.* The following statement must be included:

"All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes (*name of drug*)'s potential to increase the risk of developmental abnormalities above the background risk."

(C) *Fetal risk summary.* Under the subheading "Fetal Risk Summary," the labeling must contain a risk conclusion, contain a narrative description of the risk(s) (if the risk conclusion is based on human data), and refer to any contraindications or warnings and precautions.

(*1*) Using the risk conclusions provided in paragraphs (c)(9)(i)(C)(*2*) and (c)(9)(i)(C)(*3*) of this section, the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities in humans (i.e., structural anomalies, fetal and infant mortality, impaired physiologic function, alterations to growth) and other relevant risks (e.g., transplacental carcinogenesis). More than one risk conclusion may be needed to characterize the likelihood of risk for different developmental abnormalities, doses, durations of exposure, or gestational ages at exposure. All available data, including human, animal, and pharmacologic data, that are relevant to assessing the likelihood that a drug will increase the risk of developmental abnormalities and other relevant risks must be considered. The source(s) of the data that are the basis for the fetal risk summary must be stated. If data demonstrate that a drug is not systemically absorbed, the fetal risk summary must contain only the following statement, without any other risk conclusion:

"(*Name of drug*) is not absorbed systemically from (part of body) and cannot be detected in the blood.

Maternal use is not expected to result in fetal exposure to the drug."

(*2*) *Risk conclusions based on human data.* When both human and animal data are available, risk conclusions based on human data must be presented before risk conclusions based on animal data. A risk conclusion based on human data must be followed by a narrative description of the risks as described in paragraph (c)(9)(i)(C)(*4*) of this section.

(*i*) *Risk conclusions based on sufficient human data.* Sufficient human data may come from such sources as clinical trials, pregnancy exposure registries or other large scale epidemiologic studies, or case series reporting a rare event. When human data are sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities, the likelihood of increased risk must be characterized using one of the following risk conclusions: "Human data do not indicate that (*name of drug*) increases the risk of (*type of developmental abnormality or specific developmental abnormality*)." or "Human data indicate that (*name of drug*) increases the risk of (*type of developmental abnormality or specific abnormality*)."

(*ii*) *Risk conclusions based on other human data.* When human data are available but are not sufficient to use one of the risk conclusions listed in paragraph (c)(9)(i)(C)(*2*)(*i*) of this section, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high.

(*3*) *Risk conclusions based on animal data.* When the data on which the risk conclusion is based are animal data, the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities using one of the following risk conclusions:

(*i*) *Not predicted to increase the risk.* When animal data contain no findings for any developmental abnormality, the fetal risk summary must state: "Based on animal data, (*name of drug*) is not predicted to increase the risk of developmental abnormalities (see Data)."

(*ii*) *Low likelihood of increased risk.* When animal data contain findings of developmental abnormality but the weight of the evidence indicates that the findings are not relevant to humans (e.g., findings in a single animal species that are caused by unique drug metabolism or a mechanism of action thought not to be relevant to humans; findings at high exposures compared with the maximum recommended human exposure), the fetal risk summary must state: "Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be low (see Data)."

(*iii*) *Moderate likelihood of increased risk.* When animal data contain findings of one or more fetal developmental abnormalities in one or more animal species, and those findings are thought to be relevant to humans, the fetal risk summary must state: "Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be moderate (see Data)."

(*iv*) *High likelihood of increased risk.* When animal data contain robust findings of developmental abnormalities (e.g., multiple findings in multiple animal species, similar findings across species, findings at low exposures compared with the anticipated human exposure) thought to be relevant for humans, the fetal risk summary must state: "Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be high (see Data)."

(*v*) *Insufficient data.* When there are insufficient animal data or no animal data on which to assess the drug's potential to increase the risk of developmental abnormalities, the fetal risk summary must so state (see Data).

(*4*) *Narrative description of risk(s).* When there are human data, the risk conclusion must be followed by a brief description of the risks of developmental abnormalities as well as other relevant risks associated with the drug. To the extent possible, this description must include the specific developmental abnormality (e.g., neural tube defects); the incidence, seriousness, reversibility, and correctability of the abnormality; and the effect on the risk of dose, duration of exposure, and gestational timing of exposure. When appropriate, the description must include the risk above the background risk attributed to drug exposure and confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk.

(*5*) *Contraindications, warnings, and precautions.* If there is information in the "Contraindications" or "Warnings and Precautions" section of the labeling on an increased risk to the fetus from exposure to the drug, the fetal risk summary must refer to the relevant section.

(D) *Clinical considerations.* Under the subheading "Clinical Considerations," the "Pregnancy" subsection of the labeling must provide the following information:

(*1*) *Inadvertent exposure during pregnancy.* The labeling must discuss the known or predicted risks to the fetus from inadvertent exposure to the drug (exposure in early pregnancy before a woman knows she is pregnant), including human or animal data on dose, timing, and duration of exposure. If there are no human or animal data to assess the risk from inadvertent exposure, the labeling must so state.

(*2*) *Prescribing decisions for pregnant women.* The labeling must provide the following information:

(*i*) The labeling must describe the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat.

(*ii*) *Information about dosing adjustments during pregnancy must be provided.* This information must also be included in the "Dosage and Administration" and "Clinical Pharmacology" sections of the labeling. If there are no data on dosing in pregnancy, the labeling must so state.

(*iii*) If use of the drug is associated with maternal adverse reactions that are unique to pregnancy or if known adverse reactions occur with increased frequency or severity in pregnant women, the labeling must describe the adverse reactions. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction(s). The labeling must describe any interventions that may be needed (e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy).

(*iv*) If it is known or anticipated that treatment of the pregnant woman will cause a complication in the neonate, the labeling must describe the complication, the severity and reversibility of the complication, and general types of interventions, if any, that may be needed.

(*3*) *Drug effects during labor or delivery.* If the drug has a recognized use during labor or delivery, whether or not the use is stated as an indication in the labeling, or if the drug is expected to affect labor or delivery, the labeling must provide the available information about the effect of the drug on the mother; the fetus/neonate; the duration of labor and delivery; the possibility of complications, including interventions, if any, that may be needed; and the later growth, development, and functional maturation of the child.

(E) *Data.* (*1*) Under the subheading "Data," the "Pregnancy" subsection of the labeling must provide an overview

of the data that were the basis for the fetal risk summary.

(*2*) Human and animal data must be presented separately, and human data must be presented first.

(*3*) The labeling must describe the studies, including study type(s) (e.g., controlled clinical or nonclinical, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies), animal species used, exposure information (e.g., dose, duration, timing), if known, and the nature of any identified fetal developmental abnormalities or other adverse effect(s). Animal doses must be described in terms of human dose equivalents and the basis for those calculations must be included.

(*4*) For human data, positive and negative experiences during pregnancy, including developmental abnormalities, must be described. To the extent applicable, the description must include the number of subjects and the duration of the study.

(*5*) For animal data, the relationship of the exposure and mechanism of action in the animal species to the anticipated exposure and mechanism of action in humans must be described. If this relationship is not known, that should be stated.

(ii) *8.2 Lactation.* This subsection of the labeling must contain the following information in the following order:

(A) *Risk summary.* Under the subheading "Risk Summary," if, as described under § 201.57(c)(9)(ii)(A)(*1*) through (c)(9)(ii)(A)(*3*) of this section, the data demonstrate that the drug does not affect the quantity and/or quality of human milk and there is reasonable certainty either that the drug is not detectable in human milk or that the amount of drug consumed via breast milk will not adversely affect the breast-fed child, the labeling must state: "The use of (*name of drug*) is compatible with breast-feeding." After this statement (if applicable), the risk summary must summarize the drug's effect on milk production, what is known about the presence of the drug in human milk, and the effects on the breast-fed child. The source(s) of the data (e.g., human, animal, in vitro) that are the basis for the risk summary must be stated. When there are insufficient data or no data to assess the drug's effect on milk production, the presence of the drug in human milk, and/or the effects on the breast-fed child, the risk summary must so state. If data demonstrate that a drug is not systemically absorbed, the fetal risk summary must contain only the following statement: "(*Name of drug*) is not absorbed systemically from (part of body) and cannot be detected in the mother's blood. Therefore, detectable amounts of (*name of drug*) will not be present in breast milk. Breast-feeding is not expected to result in fetal exposure to the drug." If the drug is absorbed systemically, the risk summary must describe the following to the extent information is available:

(*1*) *Effects of drug on milk production.* The risk summary must describe the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the milk on the breast-fed child.

(*2*) *Presence of drug in human milk.*

(*i*) The risk summary must describe the presence of the drug in human milk in one of the following ways: The drug is not detectable in human milk; the drug has been detected in human milk; the drug is predicted to be present in human milk; the drug is not predicted to be present in human milk; or the data are insufficient to know or predict whether the drug is present in human milk.

(*ii*) If studies demonstrate that the drug is not detectable in human milk, the risk summary must state the limits of the assay used.

(*iii*) If the drug has been detected in human milk, the risk summary must give the concentration detected in milk in reference to a stated maternal dose (or, if the drug has been labeled for pediatric use, in reference to the labeled pediatric dose), an estimate of the amount of the drug consumed daily by the infant based on an average daily milk consumption of 150 milliliters per kilogram of infant weight per day, and an estimate of the percent of the maternal dose excreted in human milk.

(*3*) *Effects of drug on the breast-fed child.* The risk summary must contain information on the likelihood and seriousness of known or predicted effects on the breast-fed child from exposure to the drug in human milk. The risk summary must be based on the pharmacologic and toxicologic profile of the drug, the amount of drug detected or predicted to be found in human milk, and age-related differences in absorption, distribution, metabolism, and elimination.

(B) *Clinical considerations.* Under the subheading "Clinical Considerations," the labeling must provide the following information to the extent it is available:

(*1*) Information concerning ways to minimize the exposure of the breast-fed child to the drug, such as timing the dose relative to breast-feeding or pumping and discarding milk for a specified period.

(*2*) Information about potential drug effects in the breast-fed child that could be useful to caregivers, including recommendations for monitoring or responding to these effects.

(*3*) Information about dosing adjustments during lactation. This information must also be included in the "Dosage and Administration" and "Clinical Pharmacology" sections.

(C) *Data.* Under the subheading "Data," the "Lactation" subsection of the labeling must provide an overview of the data that are the basis for the risk summary and clinical considerations.

* * * * *

§ 201.80 [Amended]

4. Amend § 201.80 as follows:

a. Remove the paragraph heading "Pregnancy category A." and the words "Pregnancy Category A." from paragraph (f)(6)(i)(*a*);

b. Remove the paragraph heading "Pregnancy category B." and the words "Pregnancy Category B." both times they appear from paragraph (f)(6)(i)(*b*);

c. Remove the paragraph heading "Pregnancy category C." and the words "Pregnancy Category C." both times they appear from paragraph (f)(6)(i)(*c*);

d. Remove the paragraph heading "Pregnancy category D." and the words "Pregnancy Category D." from paragraph (f)(6)(i)(*d*); and

e. Remove the paragraph heading "Pregnancy category X." and the words "Pregnancy Category X." from paragraph (f)(6)(i)(*e*).

[This appendix will not appear in the Code of Federal Regulations.]

APPENDIX

This appendix contains examples of how to apply the proposed rule depending on the type of data available. All examples use hypothetical drugs.

SAMPLE PREGNANCY SUBSECTION LABELING

1. Drug for which only animal data are available; with developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes ALPHATHON's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on animal data, the likelihood that ALPHATHON increases the risk of developmental abnormalities is predicted to be high (see Data).

Clinical Considerations

Asthma complicates approximately 1 percent of all pregnancies resulting in higher perinatal mortality, low birth weight infants, preterm births, and pregnancy-induced hypertension compared to outcomes for nonasthmatic women. Because of the risks of even mild maternal hypoxia to the developing fetus, asthma should be clinically well-controlled during pregnancy. There are no human studies evaluating ALPHATHON use in pregnant women. The time of gestation at which risk may be greatest is unknown; therefore, risks of inadvertent exposure in early gestation cannot be evaluated. Animal data suggest that ALPHATHON exposure may result in early fetal loss and anomalies of major organ systems. There are no data regarding dose adjustment needs in pregnancy. Given the lack of human data and the risks suggested by animal data, prescribers should consider alternative treatments for asthma for pregnant women when possible (especially during the first trimester) and women planning pregnancy.

Data

Human data.

- There are no data on human pregnancies exposed to ALPHATHON.

Animal Data.

- Reproductive studies performed during early pregnancy in rats at oral doses 0.75 to 1.0 times the recommended human dose (adjusted for body surface area) showed implantation loss, fetal resorptions, and major congenital anomalies of the cardiac, skeletal and renal systems without signs of maternal toxicity.
- Reproductive studies performed in early pregnancy in rabbits at doses approximately 0.33 to 1.0 times the recommended human dose (adjusted for body surface area) showed increased post-implantation loss. Studies at 3 times the human dose showed significant fetal loss without signs of maternal toxicity.
- The effects of ALPHATHON on fetal growth, labor, or post-natal complications were not evaluated in the animal studies.

2. Drug for which only animal data are available; lack of developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes GAMMAZINE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on animal data, GAMMAZINE is not predicted to increase the risk of developmental abnormalities.

Clinical Considerations

Infection of the urinary tract in pregnant women carries a higher risk of morbidity than in the general population and is associated with an increased incidence of preterm delivery, low birth weight, and progression to pyelonephritis. It is not known whether the dose of GAMMAZINE requires adjustment during pregnancy.

Data

Human Data.

- There are no data on human pregnancies exposed to GAMMAZINE.

Animal Data.

- No teratogenic effects were seen when pregnant rats and rabbits were treated throughout pregnancy with doses equivalent to 1.5 times the maximum recommended human dose adjusted for body surface area. There were no findings of increased fetal loss, mortality or resorptions, reductions in body weights in fetuses, or other developmental abnormalities.

3. Drug for which animal and some human (insufficient) data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes KAPPAATE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on limited human data from one retrospective cohort study and postmarketing adverse event reporting, the likelihood that KAPPAATE increases the risk of major congenital abnormalities or spontaneous abortions is low. Short term (less than 3 weeks), first trimester exposure to 5 to 10 milligrams per (mg/) day of KAPPAATE did not result in an increase in major congenital abnormalities or spontaneous abortions over the background rate. The limited number of pregnant women that were exposed to KAPPAATE during the second and third trimesters delivered infants with no major congenital abnormalities. Based on animal data, the likelihood that KAPPAATE increases the risk of developmental abnormalities is predicted to be moderate.

Clinical Considerations

Symptoms of heartburn and gastroesophageal reflux disease (GERD) are common during pregnancy, occurring in about 50 percent of women in the third trimester. During pregnancy, untreated GERD can lead to reflux esophagitis and can increase nausea and asthma exacerbations in asthmatics. Based on limited human data, inadvertent exposure to KAPPAATE in early pregnancy is unlikely to be associated with major congenital abnormalities or spontaneous abortions; however, animal data suggest that early fetal loss may result from KAPPAATE exposure. Pharmacokinetic studies have shown that no dose adjustment of KAPPAATE is needed for pregnant women in the third trimester (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY). Pharmacologically similar drugs have demonstrated delayed parturition in animal studies, but the relevance of this finding in humans is not known.

Data

Human Data.

- A retrospective cohort study reported on 400 pregnant women who used 5 to 10 mg/day of KAPPAATE in the first trimester.[1] The majority of use (90 percent) was short term (less than 3 weeks). The overall malformation rate for first trimester exposure to KAPPAATE was 3.4 percent (95 percent CI 1.3-7.2) compared to 4.1 percent (95 percent CI 1.6-6.2) in the comparator group. The study could effectively rule out a relative risk greater than 2.0 for overall malformations. Rates of spontaneous abortions did not differ between the groups.
- Postmarketing reports on 125 women exposed to 5 to 10 mg/day of KAPPAATE during pregnancy did not suggest an increased risk of major congenital malformations compared to the background rate in the general population. However, gestational ages and durations of exposure were not available for all cases. Interpretation of these results are limited by the voluntary nature of postmarketing adverse event reporting and underreporting.
- No change in pharmacokinetics were seen in pregnant women at 32 to 36 weeks gestation given a single dose of KAPPAATE (see CLINICAL PHARMACOLOGY).

Animal Data.

- In rats, no teratogenic or embryocidal effects were observed when KAPPAATE was administered at doses up to 7 times the human dose on a body surface area basis).
- In rabbits, KAPPAATE at maternal doses about 5 to 50 times the human dose on a body surface area basis produced dose-related increases in embryo-lethality, fetal resorptions,

[1] Smith J.D., M.R. Perkins, "Retrospective study on pregnant women exposed to Kappaate," *Some Medical Journal*, 121(55):123–134, 2002.

pregnancy disruptions, and fetal growth impairment.

- No effects were seen on parturition.

4. Drug for which sufficient human data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Deltaman's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Human data do not indicate that DELTAMAN increases the overall risk of congenital malformations or neural tube defects. The majority of reported human exposures to DELTAMAN are first trimester exposures. Epidemiology studies adequate to detect a 2.5-fold increase in the rate of major malformations and a 10-fold increase in the rate of neural tube defects did not detect a risk. Based on animal data, the likelihood that DELTAMAN increases the risk of other developmental abnormalities is predicted to be low.

Clinical Considerations

About 1 in 100 women of childbearing age has diabetes. During pregnancy, diabetic women have increased risks of miscarriage, preterm labor, stillbirth, macrosomia, and congenital malformations, including heart defects and neural tube defects. Neonates born to women with poorly controlled diabetes are at increased risk of breathing difficulties, low blood sugar levels and jaundice. Based on human data, inadvertent exposure to DELTAMAN in early pregnancy is not associated with an increased risk of major congenital abnormalities or neural tube defects. There are no data regarding whether dosing adjustments are needed when DELTAMAN is used in pregnancy.

Data

Human Data.

- The DELTAMAN Pregnancy Exposure Registry, a population-based prospective cohort epidemiological study, has collected data since January 2000. As of December 2007, the registry documented outcomes on 1,055 infants exposed to DELTAMAN during pregnancy (997 exposed during the first trimester and 58 exposed after the first trimester) have been documented. In utero exposure to DELTAMAN was not associated with an increased risk of major congenital malformations at birth (odds ratio 0.93, 95 percent CI 0.52-1.39). The number of infants born with neural tube defects was similar in the DELTAMAN exposed infants and controls. The sample size in this study had 90 percent power to detect a 2.5-fold increase in the rate of major malformation and 80 percent power to detect a 10-fold increase in the rate of neural tube defects.
- A retrospective cohort study reported on 869 pregnant women exposed to either DELTAMAN or pharmacologically similar drugs in the first trimester (245 exposed to DELTAMAN).[2] The overall major malformation rate was 4.1 percent (95 percent CI 3.2-5.1) and the malformation rate for first trimester exposure to DELTAMAN was 3.4 percent (95 percent CI 1.3-7.8). The relative risk of major malformations associated with first trimester exposure to DELTAMAN compared with nonexposed women was 0.92 (95 percent CI 0.34-2.3). The sample size in this study had 80 percent power to detect a 4-fold increase in the rate of major malformations.

Animal Data.

- Exposure of pregnant rats or mice to DELTAMAN at doses comparable to the maximum recommended human dose (based on body surface area) resulted in embryonic death and malformations in the offspring. Skeletal abnormalities were the most common malformations observed in rats and cardiac, skeletal and urinary tract abnormalities were seen most often in mice. Neural tube defects were observed in pregnant mice and rats at doses of 15 to 25 and 5 to 20 times the human dose (based on body surface area), respectively. Behavioral alterations and poor weight gain were seen among the offspring of rats treated with DELTAMAN during pregnancy at doses greater than 15 times the maximum human dose (based on body surface area).
- Studies in cynomolgus monkeys at 1 to 10 times the maximum recommended human dose (based on a body surface area) demonstrated a dose dependent increase in neural tube and skeletal anomalies.

SAMPLE LACTATION SUBSECTION LABELING

1. Drug for which no data are available:

Risk Summary

No studies have been conducted to assess ALPHAZINE's impact on milk production, its presence in breast milk or its effects on the breast-fed child.

Clinical Considerations

Other medical therapies are available for the treatment of maternal hypertension.

Data

No data available.

2. Drug for which pharmacologic class information is available, but no human data are available:

Risk Summary

No studies have been conducted to assess THETAM's effect on milk production, its presence in breast milk, or its effects on the breast-fed child. Based on experience with other products in this class, maternal THETAM use has the potential to cause neutropenia in the breast-fed child. Because of the potential for neutropenia in the breast-fed child, a decision should be made whether to discontinue breast-feeding or discontinue using THETAM.

Clinical Considerations

Other medical therapies are available for the treatment of maternal fungal infection.

Data

No data available.

3. Drug for which human data are available:

Risk Summary

GAMMATOL is secreted in human milk. At a maternal dose of 400 mg daily, the average milk concentration, collected over 24 hours after dosing, was 10 mcg/milliliter (mL) which is lower than maternal serum drug concentrations at steady state. Based on an average milk consumption of 150 mL/kilogram (kg)/day, a 2-month-old infant would consume approximately 6 mg/day of GAMMATOL via breast milk, which is approximately 1.3 percent of the maternal dose. No studies have been performed to assess infant absorption and exposure to GAMMATOL from breast milk. No studies have been performed to assess the impact of GAMMATOL on milk production or its effects on the breast-fed child.

Clinical Considerations

Because GAMMATOL is taken once daily, mothers can reduce infant exposure by taking their GAMMATOL dose immediately after breast-feeding at the time of day when feedings are less frequent.

Data

- A lactation study was performed in 30 women who were 2 months postpartum and exclusively breast-feeding their infants. All women enrolled in the study were taking a 400 mg single dose of GAMMATOL daily. Breast milk samples were collected from each breast at the beginning and end of each feeding for 24 hours after a GAMMATOL dose. An average

[2] Jones A.B. and C.D. Smith, "Exposure to Deltaman during pregnancy," *Medical Journal*, 98:56–68, 2000.