DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling;

Final Rule

Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467)

Final Regulatory Impact Analysis

Final Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

For this final regulatory impact analysis, we use the following terms: "drug" refers to a human prescription drug or biological product regulated as a drug; "PLR labeling" refers to prescription drug labeling subject to 21 CFR §201.57(c)(9); "non-PLR labeling" refers to prescription drug labeling subject to 21 CFR §201.80(f)(6)-(8); "branded drug" refers to a human prescription drug approved under a new drug application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), or a human biological drug product licensed under a biologics license application under section 351 of the Public Health Service Act; and "generic drug" refers to a human prescription drug approved under an abbreviated new drug application under section 505(j) of the FD&C Act.[1]

The 2006 Physician Labeling Rule (PLR) did not require changes to the content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of human prescription drug labeling. The Pregnancy and Lactation Labeling Rule (PLLR) will require that applicants with PLR labeling comply with new content and format requirements. The "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section will be replaced by the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections. New information will be required to summarize the key information needed by health care providers treating females and males of reproductive potential. The information in these subsections will be

[1] These terms are used only for ease of reference and estimates in this regulatory impact analysis. These terms are not intended to be regulatory definitions and may be inconsistent with terms used in other contexts. A "generic drug product," for example, may have a brand name, but it is not considered a "branded drug" for purposes of this regulatory impact analysis.

presented in a narrative, following a standardized order and format with clear subheadings. The final rule will also require that applicants with non-PLR labeling remove the pregnancy category, but not the required statement that describes the category.

As described in the preamble, the "Pregnancy" subsection will include the following information:

- If there is a scientifically acceptable pregnancy exposure registry, a standard statement about the pregnancy exposure registry, and contact information for the registry.
- Risk summary including a description of the background risk of major birth defects and miscarriage.
- Clinical considerations aimed specifically at information health care providers need to make prescribing decisions and counsel patients.
- Discussion of the data underlying the risk summary and clinical considerations.

Furthermore, as described in the preamble, the "Lactation" subsection will include the following information:

- Risk summary including a risk-benefit statement (unless breastfeeding is contraindicated during drug therapy).
- Clinical considerations.
- Discussion of the data underlying the risk summary and clinical considerations.

To minimize unnecessary clutter in the labeling, when certain information is unavailable the final rule allows applicants to eliminate certain subheadings, including "Pregnancy Exposure Registry" in the "Pregnancy" subsection, "Clinical Considerations" in both the "Pregnancy" and

"Lactation" subsections, and "Data" in both the "Pregnancy" and "Lactation" subsections. When pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest potential drug-associated fertility effects, the final rule will require that the "Females and Males of Reproductive Potential" subsection include this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility."

By addressing issues raised by experts and stakeholders, the final rule will improve the content of the affected subsections of prescription drug labeling and require that the content follow a standardized order and format. Over 10 years and with a 7 percent discount rate, the present value of one-time costs of the rule equal $52.4 million and the present value of the annual costs equal $14.4 million; the present value of the total costs equal $66.8 million. The annualized costs of the rule total $9.5 million with a 7 percent discount rate. The primary goal of the final rule is to improve the quality of the affected subsections of prescription drug labeling. Better quality prescribing information can enhance the usefulness of the labeling. Any public health benefits of the final rule result from improved health outcomes. Because we have no information about how improved labeling will affect prescriber behavior and patient outcomes, we are unable to estimate the benefits of the final rule.

Table 1. Economic Data: Costs and Benefits Accounting Statement

				Units			
Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							

Annualized Monetized $millions/year					7%		
					3%		
Annualized Quantified					7%		
					3%		
Qualitative	Improved quality of prescription drug labeling for health care providers						
Costs							
Annualized Monetized $millions/year	$9.5			2011	7%	10 years	
	$9.2			2011	3%	10 years	
Annualized Quantified					7%		
					3%		
Qualitative							
Transfers							
Federal Annualized Monetized $millions/year					7%		
					3%		
From/ To	From:			To:			
Other Annualized Monetized $millions/year					7%		
					3%		
From/To	From:			To:			

Effects	
State, Local or Tribal Government: No effect	
Small Business: The final rule will have significant impacts on some small pharmaceutical manufacturers and prescription drug repackagers and relabelers.	
Wages: No effect	
Growth: No effect	

II. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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 final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because our analysis suggests that some small drug manufacturers and drug repackagers and relabelers will incur costs that total more than 1 percent of their annual income in years 3, 4, or 5, the Agency declines to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

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 $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

This final rule requires applicants with PLR labeling to remove the pregnancy category and the required statement that describes the category, if a category exists, and to comply with the new content and format requirements of certain subsections of PLR labeling. The PLR did not require changes to the content of the “Pregnancy,” “Labor and delivery,” and “Nursing mothers” subsections of the “Use in Specific Populations” section. The final rule will replace these subsections, add new narrative content and revise the content of current labeling, and require that the content follow a standardized order and format. The final rule also requires that applicants with non-PLR labeling remove the pregnancy category (e.g., “Pregnancy Category

C"), but not the required statement that describes the category, if a category exists. Table 2 shows that over 10 years with a 7 percent discount rate, the present value of one-time costs of the rule equals $52.4 million and the present value of the annual costs equals $14.4 million; with a 3 percent discount rate, the present value of one-time costs equals $60.1 million and the present value of the annual costs equals $18.2 million. The present value of the total costs equals $66.8 million with a 7 percent discount rate and $78.2 million with a 3 percent discount rate. The annualized costs of the rule total $9.5 million with a 7 percent discount rate and $9.2 million with a 3 percent discount rate. The final rule will address issues raised by experts and stakeholders and improve the quality of the affected sections of prescription drug labeling. However, we are unable to estimate the benefits of the final rule because we are unable to predict how the new labeling will change prescribing behavior or health outcomes.

Table 2. Summary of the Costs

Present Value of One-Time Costs ($ mil) (3 percent)	Present Value of Annual Costs ($ mil) (3 percent)	Present Value of Total Costs ($ mil) (3 percent)	Present Value of One-Time Costs ($ mil) (7 percent)	Present Value of Annual Costs ($ mil) (7 percent)	Present Value of Total Costs ($ mil) (7 percent)
60.1	18.2	78.2	52.4	14.4	66.8

A. Need for the Rule

The first regulations on the content and format of prescription drug labeling were established in 1979, including the requirement to assign drugs to one of five pregnancy categories. Over time, however, labeling became long, repetitive, and difficult to use. With the PLR in 2006, the Agency began to apply modern principles of effective communication to improve the quality of prescription drug labeling. However, the PLR left untouched the content

of the “Pregnancy,” “Labor and delivery,” and “Nursing mothers” subsections of the “Use in Specific Populations” section. This decision gave the Agency sufficient time to meet with experts and stakeholders to develop a regulatory framework that requires applicants to prepare content that clearly communicates available information about drugs used during pregnancy and lactation, and in females and males of reproductive potential. With this final rule, the Agency specifically addresses the content and format of these subsections.

The labeling of newly approved prescription drugs may lack some important information used by health care providers and patients to make decisions about the use of prescription drugs during pregnancy and lactation, or to understand the potential risks of prescription drugs to females and males of reproductive potential. Often, at the time of approval, the only available information relating to a drug’s use in pregnancy may be the animal reproductive toxicity studies and the pregnancy category. Currently, applicants and the Agency negotiate the pregnancy category assigned to the drug when the initial labeling is prepared; most new drugs are assigned to category C, which has become the catch all category. This category is especially problematic because a drug can be assigned to this category for different reasons including the lack of human and animal data, or if the benefits of the drug outweigh the potential fetal risks identified in animal studies and there are no adequate and well-controlled clinical studies in pregnant women. Health care providers can make incorrect assumptions about the use of a drug during pregnancy when they misunderstand or misinterpret the pregnancy category. Consequently, categories alone have limited value.

The primary objectives of the final rule are to improve labeling by updating the content and format of these subsections of prescription drug labeling, and to eliminate the pregnancy category system. Consistent with the approach taken by the PLR, the Agency provides

applicants with clear guidance about the required content and format by issuing along with this final rule, a draft guidance for industry on "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products--Content and Format". Following a standardized structure is essential for effective communication and will improve the quality of the labeling. Thus, for PLR labeling, the final rule will ensure that these subsections contain the most up-to-date information available and provide prescribers with clinically relevant data that they can use in their decision making processes.

B. Comments on the Initial Regulatory Impact Analysis

Although we received over 70 comments on the proposed rule, few addressed our preliminary regulatory impact analysis. We discuss those specific comments below. When possible, as discussed in our responses, we adjust our final analysis to take into account these comments.

(Comment 1) We requested comment on the costs to prepare and submit an electronic version of labeling consistent with the Extensible Markup Language-based Structured Product Labeling standard. We received comments on the process that companies will follow to code labeling elements and to prepare the Structured Product Labeling for submission. We received comments that the final rule will require a one-time effort by the industry-wide Structured Product Labeling team, the Agency and third parties to establish coding for the new pregnancy and lactation sections. In addition, each company will code the separate elements of the labeling and make any changes to existing coding that might be required. However, the costs to prepare the Structured Product Labeling for submission are the same for any electronic submission.

(Response) None of the comments included estimates of the time required or the costs to perform these actions. Without specific cost information, we are unable to quantify the

individual burden for Structured Product Labeling coding. Because companies need to code any labeling submitted to the Agency, coding is one of many actions taken when creating the new content. Thus, although the comments did not include specific time or cost estimates, our revised estimate of the burden to collect and organize new content includes coding the new content. These costs would be incurred only for PLR labeling of branded drugs. Labeling of generic drugs would use the same PLLR-specific coding as the reference listed drug specified in the abbreviated new drug application for the generic drug, and labeling submitted by repackagers and relabelers would use the same PLLR-specific coding as the manufacturers of the drugs they repackage or relabel.

(Comment 2) We received comments from industry that we understated the time needed to prepare the content and format of labeling which conforms to the PLLR requirements. One commenter suggested it would take 120 hours to perform these actions for existing labeling. Another commenter suggested that it will take from 175 hours to 200 hours to prepare the new content and submit the new labeling.

(Response) We agree that our estimate of the time to prepare new content and format likely understates the actual burden for some applicants or manufacturers. However, these comments referred to the proposed Paperwork Reduction Act of 1995 section and to the preliminary regulatory impact analysis. Although the underlying data in the paperwork section comes from our preliminary analysis, the two analyses present the burden in different ways. This apparently created confusion about the basis of the analysis of impacts. In the preliminary analysis of impacts we estimate that a physician or other health care professional would spend 10 hours to collect new information and regulatory affairs and legal personnel would spend 10 hours to organize the information and to discuss the content of labeling with the Agency (73 FR

30850). Our initial estimates were based on very limited experience with labeling that incorporates information similar to the requirements of the proposed rule. The proposed paperwork section also estimates this burden is 20 hours.

We also estimate the incremental burden to revise existing labeling as an additional action required for manufacturers with existing labeling. For our preliminary analysis, we cite estimates from the PLR final regulatory impact analysis (68 FR 6074 cited at 71 FR 3976). Depending on size, we estimate that manufacturers spend an additional 22 hours to 54 hours to revise the labeling, including among other things, to perform internal review of the new content, to prepare and to proofread new artwork, to replace labeling in the production system, to prepare the Structured Product Labeling file with the new labeling and to submit the file to the Agency. The total time estimated to comply with the requirements of the PLLR ranges from 42 hours (i.e., 20 hours to collect and organize new content and 22 hours to revise existing labeling) to 74 hours (i.e., 20 hours to collect and organize new content and 54 hours to revise existing labeling). In contrast to the preliminary regulatory impact analysis, the proposed paperwork section cites 85 hours as the burden to revise existing labeling.

In general, little information about the use of the drug during pregnancy or lactation exists when an application for a branded drug is initially approved. The incremental burden to create labeling of new approvals in the PLLR format will be substantially less than the burden for drugs that have been marketed for years. We expect some trade-off of the time spent in discussions with the Agency: less time to discuss a pregnancy category and more time to discuss the narrative format and additional content. Although we agree that our initial estimate of 20 hours to prepare new content and format likely understates the actual burden for applicants or manufacturers of drugs that have been marketed for several years, we disagree with commenters

that applicants or manufacturers will spend 120 to 200 hours on future approvals. For the final analysis of impacts, therefore, we apply an adjustment factor to our initial estimate of 20 hours for future approvals. Multiplying 20 hours by 2.1 (175 hours from comments /85 hours from the proposed paperwork section) gives us a lower bound estimate of about 40 hours. For existing labeling of branded drugs, we use the 120 hours suggested in comments on the proposed paperwork section.

(Comment 3) We received one comment that our hourly wage rate of $25.65 was substantially below average industry wages, based on our estimate that a large manufacturer would spend $2,180 in labor to prepare and submit revised labeling.

(Response) The commenter misunderstood our analysis and assumed that we used 85 hours as the basis for our calculations. In our initial analysis of impacts we cite the following average hourly wages to collect and organize the new content: $100 for medical personnel, and $50 for regulatory affairs and legal personnel (73 FR 30850.) To estimate the costs to revise existing labeling, we use estimates cited in our final analysis of impacts for PLR (68 FR 6062 at 6074 cited at 71 FR 3976). For example, a large manufacturer would have regulatory affairs personnel spend 34 hours and manufacturing personnel spend 20 hours to revise existing labeling. Using the 2004 hourly wages of $50 for regulatory affairs and $24 for manufacturing personnel, we estimated the labor needed to revise labeling would cost a large manufacturer about $2,180. For our final regulatory impact analysis, we keep our original estimate of the number of hours needed to revise existing labeling and update our wage estimates with 2011 industry-specific hourly wages from the Bureau of Labor Statistics (Ref. 1).

(Comment 4) A comment from industry suggests that the costs to establish and maintain a pregnancy registry throughout a product's life cycle should be included in the impact analysis.

(Response) The final rule only requires that the labeling include registry information if there is a scientifically acceptable registry. Manufacturers make the decision to establish and maintain a registry. We disagree that these costs should be considered because the costs or decisions are beyond the scope of this rulemaking. Consequently, we do not include registry costs in our final impact analysis, although the existence of a registry can affect the incremental labeling costs we estimate.

(Comment 5) One comment from an industry association stated that the analysis of impacts should include the burden to develop the risk summary when no appropriate comparators exist.

(Response) Our preliminary regulatory impact analysis included an estimate of 20 hours for applicants to collect and organize the information required by the final rule. This estimate includes the time to develop the risk summary. As discussed previously, in response to comments, for our final regulatory impact analysis we have increased our estimate of the time required to collect and organize data.

C. Costs of the Final Rule

The level of effort needed to comply with the requirements of the final rule will depend on whether the labeling is PLR labeling or non-PLR labeling, and the length of time the drug has been marketed. The final rule will require that applicants of drugs with PLR labeling modify the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling, including removing the pregnancy category and the required statement that describes the category, if a category exists. Applicants of drugs with non-PLR labeling will must remove the pregnancy category, but not the required statement that describes the category, if a category exists.

Similar to the implementation plan for PLR (71 FR 3928,) applicants of new drug applications, biologics license applications, or certain efficacy supplements submitted on or after the PLLR effective date must conform to the requirements of this final rule at the time when the application is submitted. Applicants of applications pending on the effective date of this rule must conform to the requirements of the final rule by year 4 or at the time of approval, whichever is later. Approved applications must follow the implementation plan described in the preamble and in table 3 of this document. Labeling of generic drugs must conform to the labeling of their reference listed drug. Our analysis assumes that applicants of generic drugs will modify labeling at the same time as the applicant of the reference listed drug. Moreover, relabelers and repackagers must modify their labeling and we assume that these companies will follow the same schedule as the applicants of the drugs they relabel or repackage.

Table 3. Implementation Plan

Trigger Dates[1]	When Labeling Must Conform to the Final Rule	Requirements of Final Rule
Prior to June 30, 2001 (non-PLR labeling)	3 years	§§201.80(4)(a) - (e)
June 30, 2001, up to and including June 29, 2002; June 30, 2005, up to an including June 29, 2007 (PLR labeling)	3 years	§§201.57(c)(9)(i) - (iii)
June 30, 2007, up to and including the effective date (PLR labeling)	4 years	§§201.57(c)(9)(i) - (iii)
June 30, 2002, up to and including June 29, 2005 (PLR labeling)	5 years	§§201.57(c)(9)(i) - (iii)

[1] Trigger date refers to the most recent approval date of an application for a branded drug or to the most recent approval date of an application for the reference listed drug of a generic drug.

1. Affected Applications

We have updated our initial analysis to include applications and efficacy supplements approved from June 30, 2001 to June 30, 2012. Efficacy supplements account for over 40

percent of the total number of approvals during this period, with some applications having multiple efficacy supplements. In these cases, there can be multiple trigger dates for a specific application. To avoid double counting, we use only the most recent application approval date as the PLLR trigger date.

Although initial approvals of generic drugs can follow the approval of the reference listed drug by several or more years, for our analysis we use the most recent approval date of the reference listed drug as the PLLR trigger date for generic drugs. Eleven years of data on labeling that conforms to the requirements of PLR give us better information to estimate the number of affected generic drugs. We take the same approach for repackagers and relabelers because they are not responsible for the content of the prescription drug labeling.

Finally, the level of effort varies by type of labeling (e.g., branded drug labeling, generic drug labeling, and labeling of repackaged or relabeled drugs) and between existing labeling and new labeling. For each type of labeling, we divide our estimate of affected applications into future applications, pending applications and existing applications approved on or after June 30, 2001, and applications approved before June 30, 2001.

a. Branded Drug Labeling. We consider new drug applications, biologics license applications, and certain efficacy supplements submitted after the effective date of this final rule as future approvals. Even though the number of future approvals is unknown, we use the average annual number of applications for branded drugs approved between June 30, 2001 and June 30, 2012, as a proxy for the number of future approvals. To avoid overstating this number, for drugs with multiple applications (e.g., multiple efficacy supplements for the same application number), we use the newest approval date as the PLLR trigger date. Table 4 shows that in the 10

years following the effective date of the final rule, we estimate that applicants will receive approvals that trigger PLLR for, on average, about 800 branded drugs (i.e., future approvals).

Applicants with approved or pending applications subject to the requirements of the PLR must change the content and format of existing PLR labeling to conform to the requirements of the PLLR final rule. To minimize the burden on industry, we give applicants of these approved or pending applications from 3 to 5 years (or more, if an application pending on the effective date is approved more than 5 years after that effective date) to revise their labeling to conform to the PLLR requirements. Applicants of about 1,080 applications for branded drugs would need to revise existing labeling in years 3, 4 and 5.

The final rule will require that applicants of branded drugs with non-PLR labeling make minor revisions to the "Pregnancy" subsection of the labeling to remove the pregnancy category, but not the required statement that describes the category. This provision of the final rule affects any approved branded drug with non-PLR labeling containing a pregnancy category. Although the actual number of applications that are affected by this provision of the final rule is uncertain, the recent analysis of FDA's approval data suggests that applicants will make minor revisions to existing labeling of about 1,340 branded drugs. Because the labeling of many drugs initially approved before 1979 might not contain a pregnancy category, our estimate represents the upper bound for this group of applications. Moreover, it should be noted that applicants sometimes voluntarily discontinue marketing older drugs and might do so before they will be required to revise their labeling. Although the magnitude is uncertain, this natural attrition will likely reduce the number of applications that will be affected by the final rule. Applicants of branded drugs with non-PLR labeling have 3 years after the effective date of this final rule to make this change, allowing them sufficient time to coordinate this labeling revision with routine labeling activities.

Table 4. Number of Applications for Branded Drugs Affected by Provisions of the Final Rule

Year	Future Approvals	Existing Labeling Conforms to PLR	Remove Category Letter	Total
1	80	0		80
2	80	0		80
3	80	220	1,340	1,640
4	80	610		690
5	80	250		330
6	80	0		80
7	80	0		80
8	80	0		80
9	80	0		80
10	80	0		80
Total	**800**	**1,080**	**1,340**	**3,220**

b. Generic Drug Labeling. Applicants of generic drugs will change the prescription drug labeling to match the labeling of the reference listed drug for their products. For our analysis, we used Agency data to link the abbreviated new drug application to the PLLR trigger date for the application of the appropriate reference listed drug. To estimate the number of future generic drug approvals, we use Agency data to calculate the average annual number of generic drug applications that reference branded drug applications approved between June 30, 2001 and June 30, 2012. Although uncertain, we are using time frames long enough to capture many of the older branded drugs that no longer have patent protection or marketing exclusivity. For commonly prescribed branded drugs, typically several generic drugs will enter the market once the patent protection or marketing exclusivity ends. Over 10 years, table 5 shows that we estimate on average about 120 future generic drug approvals per year will have labeling that includes pregnancy and lactation sections that conform to the PLLR. Unlike applicants of future branded drugs, applicants of future generic drugs will incur no additional costs.

Similar to our method to estimate future generic drug applications, for previously approved generic drug applications we consider the PLLR trigger date of the reference listed

drug to determine the type of required labeling change and when the person responsible for the generic drug labeling must change the labeling. Based on our analysis of approval data, in years 3, 4 and 5, applicants of about 1,320 generic drugs must change the content and format of their existing generic drug labeling to match the PLLR labeling of the reference listed drug. In addition, in year 3, applicants of about 4,160 generic drugs must remove the pregnancy category, but not the required statement that describes the category, from their generic drug labeling.

Table 5. Number of Generic Drug Applications Affected by Provisions of the Final Rule

Year [1]	Future Approvals[2]	Existing Labeling Conforms to PLR	Remove Category Letter	Total
1	120	0		120
2	120	0		120
3	120	450	4,160	4,730
4	120	410		530
5	120	460		580
6	120	0		120
7	120	0		120
8	120	0		120
9	120	0		120
10	120	0		120
Total	**1,200**	**1,320**	**4,160**	**6,680**

[1] Based on the PLLR trigger year for the associated reference listed drug.
[2] No new costs will be incurred for future approvals.

c. Prescription Drug Labeling from Repackagers and Relabelers. Although we didn't include incremental costs for repackagers and relabelers in our preliminary regulatory impact analysis, we have included these costs in our final regulatory impact analysis. We use registration and listing data to estimate the number of affected applications with labeling submitted by repackagers and relabelers. These data include the application number and NDC labeler code for the supplier of the prescription drug. We use the NDC labeler code to exclude from our count of repackagers and relabelers any manufacturer that repackages or relabels drugs that they also manufacture. We use the PLLR trigger date of the application number as the

trigger date for labeling from repackagers and relabelers. The tally of labeling by type of application approved since June 30, 2001, suggests that repackagers and relabelers handle a larger share of generic drugs than branded drugs. For example, repackagers and relabelers submitted labeling for about 6,150 generic drugs while manufacturers of generic drugs submitted labeling for about 5,500 generic drugs ; submissions of prescription drug labeling by repackagers and relabelers equal about 129 percent of the submissions of prescription drug labeling by manufacturers (6,150 generic drugs from repackagers and relabelers / 5,500 generic drugs from manufacturers). In contrast, repackagers and relabelers submitted labeling for about 1,600 branded drugs , while manufacturers of branded drugs submitted labeling for about 2,200 drugs; submissions of prescription drug labeling by repackagers and relabelers equal about 60 percent of the submissions of prescription drug labeling by manufacturers (1,600 branded drugs from repackagers and relabelers / 2,200 branded drugs from manufacturers). To estimate the number of future labeling changes required by repackagers and relabelers, we adjust our estimate of the number of future branded and generic drug approvals shown in tables 4 and 5 by these percentages.

Table 6 shows that repackagers and relabelers must revise and submit prescription drug labeling for about 7,750 applications in years 3, 4, and 5, with the greatest burden occurring in year 3. Our estimate may understate the burden for repackagers and relabelers to the extent that some of these companies have not submitted labeling to the Agency. However, repackagers and relabelers can voluntarily change suppliers when market conditions warrant, and thus, routinely change labeling more frequently than drug manufacturers. The final rule will have no influence on these decisions.

Table 6. Number of Affected Labeling Changes for Repackagers and Relabelers

Year [1]	Future Approvals [2]	Existing Labeling	Total
1	200		200
2	200		200
3	200	6,080	6,280
4	200	1,060	1,260
5	200	610	810
6	200		200
7	200		200
8	200		200
9	200		200
10	200		200
Total	**2,000**	**7,750**	**9,750**

[1] Based on the PLLR trigger year for the application number.
[2] Includes about 60 percent of future approvals in table 4 and about 129 percent of the future approvals in table 5. No new costs will be incurred for future approvals.

2. Costs to Modify Labeling.

a. <u>One-time costs.</u> We separate the one-time labeling costs into two major components: (1) The costs to collect and organize the additional information required by the rule, and (2) the costs to revise existing labeling to add or remove information. Which costs will be incurred by an applicant or persons responsible for labeling depend on (1) whether the application is subject to the PLR, (2) whether the application is new, approved or pending when the PLLR becomes effective, and (3) who is responsible for the labeling change. The level of effort needed to collect and organize information will vary depending on the amount of relevant information. Persons responsible for the labeling of future new drug applications, biologics license applications, and PLR-triggering efficacy supplements will incur only the costs to collect and organize information. Persons responsible for existing non-PLR labeling will incur only the costs to revise existing labeling to remove the pregnancy category, but not the required statement

that describes the category. Persons responsible for generic drug labeling, repackagers and relabelers will incur only the costs to revise existing labeling to incorporate any changes from the reference listed drug labeling. Persons responsible for the labeling of approved or pending new drug and biologics license applications subject to PLR will incur both costs.

i. *One-time costs to collect and organize the new content*. Under the current system, applicants and the Agency review any existing animal and human data and determine the applicable pregnancy category according to the regulations. Although the final rule will no longer require that a drug be assigned a pregnancy category, preparing the new labeling content will require more time than manufacturers currently spend preparing this part of the prescription drug labeling. For the preliminary regulatory impact analysis, we estimated that applicants would spend on average up to 20 hours to prepare and organize this new content and in discussions with the Agency. As discussed previously, we received comments on the proposed paperwork section that the time required to perform these actions was understated in the initial analysis of impacts and have adjusted our estimate based on these comments. For our final analysis, we use the lower bound estimate of 40 hours for future approvals and the upper bound of 120 hours for existing applications with PLR labeling. Because the final rule does not require submission of clinical data that the Agency must review, applicants of branded drugs who submit prior approval supplements to comply with the content and format requirements of the final rule will not incur user fees. In addition, applicants of generic drugs who submit changes being effected zero labeling supplements will not incur user fees. Using an average fully loaded wage of $121 per hour, table 7 shows the lower and upper bound estimates range from about $4,840 to $14,520.

Table 7. Revised Unit Cost to Collect and Organize Content

	Number of Hours to Collect and Organize Content	Cost to Collect and Organize Content
Future Approvals	40	$4,840
Existing Labeling	120	$14,520

As shown in table 8, industry will spend about $29.9 million in current dollars over 10 years. Most of this burden will occur in years 3, 4, and 5 when applicants or manufacturers of branded drugs add the new content and format to existing prescription drug labeling. Manufacturers of generic drugs, repackagers and relabelers merely duplicate the content of the reference listed drug labeling and will not incur any of these costs.

Table 8. Cost to Collect and Organize Content

Year	Total Number Affected[1]	One-Time Cost to Collect and Organize Information ($ mil)
1	80	0.4
2	80	0.4
3	300	5.7
4	690	15.1
5	330	6.4
6	80	0.4
7	80	0.4
8	80	0.4
9	80	0.4
10	80	0.4
Total	**1,880**	**29.9**

[1] Equals the sum of future approvals and existing labeling from table 4.
Numbers may not sum due to rounding.

ii. *One-time costs to revise existing prescription drug labeling*. As explained in our initial analysis of impacts, the Agency has previously estimated the cost of revising prescription drug labeling (68 FR 6062 at 6074, February 6, 2003). These costs vary with the size of the

company revising the labeling. In a manufacturing company, prescription drug labeling involves many departments, 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. Generic drug manufacturers have costs similar to small branded drug manufacturers. Repackagers and relabelers likely spend less time than a small manufacturer, because they don't manufacture drugs and likely have fewer interdepartmental meetings to coordinate a labeling change.

Although in our preliminary regulatory impact analysis we cited the detailed data underlying our initial analysis, we did not show the number of hours used to generate the dollar estimate. Table 9 presents the number of hours underlying our cost estimate by size of the firm and the type of employee. In addition to labor costs, companies incur material costs for each change to labeling, including artwork and labeling scrap.

Table 9. Labor to Revise Existing Labeling by Occupation and Company Type

	Small Branded Drug Manufacturer (hours)	Medium Branded Drug Manufacturer (hours)	Large Branded Drug Manufacturer (hours)	Generic Drug Manufacturer (hours)	Repackager and Relabeler (hours)
Regulatory Affairs Personnel	18	26	34	18	4
Production Personnel	4	8	20	4	4

May 2011 occupational specific wage data from BLS for the pharmaceutical preparation industry list a mean hourly wage of $60.33 for occupational code 29-1051 (pharmacists) and a mean hourly wage of $30.64 for occupational code 51-1011 (first line production manager.) Adding 100 percent for benefits and overhead, we assign a mean hourly wage of $121 to regulatory affairs employees and a mean hourly wage of $62 to production employees. Material

costs include new artwork and scrap inventory. We adjust our initial material costs for inflation from 2004 to 2011 using the GDP deflator. Table 10 shows that the one-time cost to modify existing labeling ranges from $1,340 for repackagers and relabelers to $7,770 for large manufacturers of branded drugs.

Table 10. Unit Costs to Revise Existing Labeling by Type of Company

	Small Branded Drug Manufacturer ($)	Medium Branded Drug Manufacturer ($)	Large Branded Drug Manufacturer ($)	Generic Drug Manufacturer ($)	Repackager and Relabeler ($)
Labor	2,430	3,650	5,360	2,430	740
Material	610	1,690	2,420	610	610
Total Unit Cost	**3,030**	**5,340**	**7,770**	**3,030**	**1,340**

Numbers may not sum due to rounding.

Table 11 shows the total cost to revise existing prescription drug labeling. Companies will incur these costs in years 3, 4, and 5, with year 3 having the highest burden. The cost to revise existing labeling totals $44.9 million. Although more labeling will be revised by generic drug manufacturers, repackagers and relabelers, branded drug manufacturers account for the largest share of these costs because they have higher unit costs.

Table 11. Total Costs to Revise Existing Prescription Drug Labeling

Year	Number of Affected Labeling for Branded Drugs	Number of Affected Labeling for Generic Drugs	Number of Affected Labeling for Repackagers and Relabelers	Cost to Revise Labeling for Branded Drugs [1] ($ mil)	Cost to Revise Labeling for Generic Drugs ($ mil)	Cost to Revise Labeling for Repackager and Relabeler ($ mil)	**Total Cost ($ mil)**
1	0	0	0	0.0	0.0	0.0	0.0
2	0	0	0	0.0	0.0	0.0	0.0
3	1,560	4,610	6,080	11.6	14.0	8.1	33.7
4	610	410	1,060	4.5	1.2	1.4	7.2
5	250	460	610	1.9	1.4	0.8	4.1
6	0	0	0	0.0	0.0	0.0	0.0
7	0	0	0	0.0	0.0	0.0	0.0
8	0	0	0	0.0	0.0	0.0	0.0
9	0	0	0	0.0	0.0	0.0	0.0

10	0	0	0	0.0	0.0	0.0	0.0
Total	**2,420**	**5,480**	**7,750**	**18.0**	**16.6**	**10.4**	**44.9**

[1] Based on a weighted average unit cost of $7,420.
Numbers may not sum due to rounding.

iii. *One-time cost to prepare artwork for prescription drug labeling other than trade labeling (nontrade labeling).* In contrast to trade labeling (labeling on or within the package from which the drug is to be dispensed), the PLR requires that labeling disseminated in other nontrade contexts be printed in a minimum of 8-point type size (§ 201.57(d)(6)). In our initial impact analysis, we assumed that manufacturers of affected branded drugs will incur an additional one-time cost to create new artwork for existing labeling. The new artwork is needed to fit the new pregnancy and lactation information in the 8-point type size. In contrast, new approvals have no additional costs because that artwork has not yet been created. We received no comments on this part of our analysis and merely update our initial estimate to 2011 dollars with the GDP deflator. In 2011 dollars, we estimate that, on average, manufacturers might spend $2,200 for each of the 1,080 affected branded drugs. Manufacturers will incur one-time costs equaling about $2,4 million, with $0.5 million in year 3, $1.3 million in year 4, and $0.6 million in year 5.

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 final rule would increase the length of labeling. The incremental increase will depend on many factors, including the amount of available data (which is often related to how long a drug has been marketed), the known risks of the drug, and whether a pregnancy registry exists. For the proposed rule, we estimated an increase in the size of labeling of approximately 15 square inches in 6-point type size and 24 square inches in 8-point type size (78 FR 30851). Because this

estimate was based on a small number of labeling changes, we requested comment from industry on the assumptions underlying our estimate. However, we received no comments.

To better understand the current size of the labeling affected by the rule, we reviewed a random sample of labeling in the Physicians' Desk Reference that conformed to the PLR format and measured the total size of the labeling and the size of sections "8.1 Pregnancy," "8.2 Labor and delivery" and "8.3 Nursing mothers." Stratifying our data by pregnancy category, we calculated the proportion of the total surface area of the labeling needed to accommodate these sections. As noted in table 12, on average the information presented in the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections accounts for about 2.3 percent of all subsections of the labeling. In absolute surface area, excluding labeling without a category because of its small sample size, the average size of these subsections ranges from 8 square inches for Pregnancy Category B drugs to 13 square inches for Pregnancy Category X drugs. Based on these findings, we judge that our original estimate adequately captures the average increase in size because in all cases, on average, an additional 15 square inches will more than double the current size of these sections. Thus, we have not revised our initial estimate of the incremental increase in the size of labeling for the final analysis.

Table 12. Estimated Size of Labeling by Pregnancy Category

Pregnancy Category	Sample Size	Average Size of Sections 8.1-8.3 (square inches)	Average Size of Entire Labeling (square inches)	Percentage of Labeling for Sections 8.1-8.3
B	30	8.4	483.0	1.7%
C	68	11.1	457.4	2.4%
D	25	12.3	522.4	2.4%
X	10	13.0	481.2	2.7%
(blank)	3	4.4	356.9	1.2%
Total	**136**	**10.7**	**474.5**	**2.3%**

i. *Trade labeling*. Labeling must accompany all drug shipments and any drug samples distributed to health care providers. The PLR calls this trade labeling and requires that it be printed in a minimum of 6-point type size (21 CFR § 201.57(d)(6)). To conserve space, trade labeling is normally printed on both sides of the paper. We keep our initial estimate that any new content required by the final rule will add, on average, about 7.5-square inches of paper to the overall size of trade labeling. Updating for inflation, FDA estimates that manufacturers might spend $0.01 for each additional 100-square inches of labeling they produce.

We initially estimated that about 650,000 pieces of trade labeling accompany each branded drug, about 370,000 pieces of trade labeling accompany each generic drug, and about 90 million pieces of trade labeling accompany each drug sample. We received no comment on these estimates. However, according to IMS data, the total number of prescription drugs sold from manufacturers to retail and non-retail channels was about 7.5 billion "eaches" in 2011 (IMS Health, National Sales Perspective™. Year 2011, All Prescription Drug Channels, Data Extracted July 2012). IMS defines "eaches" as the number of single items such as bottles, packages, syringes or vials contained in a unit or shipping package sold by manufacturers. Furthermore, the share of prescriptions that are generic drugs has increased since we made our initial estimate. Today, generic drugs account for about 80 percent of the prescriptions dispensed annually. Adjusting for the change in this distribution and for the change in the total number of shipments, we estimate that there would be an average of about 370,000 pieces printed for each branded drug and about 510,000 pieces printed for each generic drug. Because the new content provisions of this final rule would only add about 7.5-square inches to the overall size of trade labeling, the cost of longer labeling is modest. Accounting for inflation, it costs about $0.8645 for 1,000 pieces of branded drug labeling for and about $0.9148 for 1,000 pieces of generic drug

labeling. On average, the annual incremental printing costs for prescription drug labeling increase by about $320 for branded drugs and increase by about $470 for generic drugs.

Drug sampling has fallen about 16 percent to about 76 million samples annually (Ref. 2). We assume that almost all samples are for branded drugs. Although it is unlikely that all samples would be affected by the final rule, the annual cost of longer trade labeling accompanying all 76 million samples equal about $65,700 (76 million samples x $.0001153 per sample). Thus, this estimate represents an upper bound for the incremental costs of labeling accompanying drug samples.

ii. *Nontrade labeling*. The PLR requires that any nontrade labeling (i.e., prescription drug labeling distributed with promotional materials) be printed in a minimum of 8-point type size. We initially estimated the paper needed to print nontrade labeling increases by approximately 24 square inches. We received no comment on this estimate and thus keep it for the final analysis, but adjust the incremental material costs for longer labeling with the GDP deflator.

There are many situations where a manufacturer's representative will distribute nontrade labeling directly to healthcare professionals. These include their place of business, conferences and meetings, and continuing education programs. There are approximately 680,000 physicians in office-based practice in the United States (Ref. 2). We use this number as a rough estimate of the number of pieces of nontrade labeling distributed to healthcare professionals. For each affected branded drug, we estimate that applicants will distribute about 680,000 pieces of nontrade labeling with promotional materials in the first year that an applicant adds new content to the labeling. In each of the next 2 years, about 620,000 additional pieces of nontrade labeling

would be distributed with promotional materials. Thus we anticipate that manufacturers will print approximately 1.9 million pieces of nontrade labeling for each branded drug that has existing labeling conforming to the PLR. In total, for each of these branded drugs, nontrade labeling will increase by about 46 million additional square inches (24 square inches x 1,920,000 pieces of nontrade labeling). As discussed in section II.C.2.b.i, after adjusting for inflation we estimate that manufacturers will spend about $0.01 for each additional 100 square inches of labeling, approximately equal to the incremental increased size of 4 pieces of nontrade labeling. On average, nontrade labeling will cost manufacturers about $5,310 for each branded drug affected by the content and format requirements of the final rule (46,080,000 square inches x $0.00011527 per square inch).

iii. *Physicians' Desk Reference costs*. For the proposed rule, we estimated the costs to print longer labeling in the Physicians' Desk Reference. Since that time, the ownership of this publication has changed. The current owner offers electronic labeling information and a suite of other electronic services to the health care industry. Although about 500,000 copies of the print version of the Physicians' Desk Reference are still produced each year, manufacturers no longer pay a separate fee to include their prescription drug labeling in the traditional print version. Our understanding is that manufacturers now base their contractual decisions on other electronic services they receive. We lack information on the cost to store and deliver electronic labeling, but expect that the incremental costs incurred under the PLLR would be negligible. Consequently, we exclude from our final impact analysis the cost of printing longer labeling in the Physicians' Desk Reference.

iv. *Summary of annual costs to print longer labeling*. Based on our estimates of the number of future approvals and existing labeling that will include the new content and format required by the final rule, we estimate that over 10 years, manufacturers or repackagers and relabelers would incur incremental printing costs for about 13.2 billion pieces of trade labeling and about 2.4 billion pieces of nontrade labeling included with promotional materials (see table 13). Our assumption that manufacturers will produce nontrade labeling for every affected branded drug may overstate the number of pieces of nontrade labeling; however, we lack information to adjust our estimate. We also lack information to separate the number of pieces of trade labeling that repackagers and relabelers will print from our global estimate.

Table 13. Estimated Number of Pieces of Labeling

Year	Trade Labeling Accompanying Branded Drugs (million pieces)	Trade Labeling Accompanying Generic Drugs (million pieces)	Trade Labeling Accompanying Drug Samples (million pieces)	Nontrade Labeling Accompanying Promotional Materials (million pieces)
1	30	60	76	54
2	60	120	76	104
3	170	410	76	254
4	420	680	76	655
5	540	980	76	652
6	570	1,040	76	259
7	600	1,100	76	104
8	630	1,160	76	104
9	660	1,220	76	104
10	690	1,290	76	104
Total	**4,370**	**8,060**	**760**	**2,394**

The incremental printing costs for trade and nontrade labeling are shown in table 14. Over 10 years, the annual costs range from $0.3 million in year 1 to $2.7 million in year 10.

Table 14. Annual Costs to Print Longer Prescription Drug Labeling

Year	Trade Labeling Accompanying Branded Drugs ($ mil)	Trade Labeling Accompanying Generic Drugs ($ mil)	Trade Labeling Accompanying Drug Samples ($ mil)	Nontrade Labeling Accompanying Promotional Materials ($ mil)	**Total ($ mil)**
1	0.0	0.1	0.1	0.2	**0.3**
2	0.1	0.1	0.1	0.3	**0.5**
3	0.1	0.4	0.1	0.8	**1.4**
4	0.4	0.6	0.1	1.9	**3.0**
5	0.5	0.9	0.1	2.3	**3.8**
6	0.5	1.0	0.1	1.9	**3.4**
7	0.5	1.0	0.1	0.9	**2.4**
8	0.5	1.1	0.1	0.4	**2.1**
9	0.6	1.1	0.1	0.4	**2.2**
10	0.6	1.2	0.1	0.8	**2.7**
Total	**3.8**	**7.4**	**0.7**	**10.0**	**21.8**

Numbers may not sum due to rounding.

3. Summary of Costs for the Final Rule.

Table 15 summarizes the total costs of the final rule. Over 10 years, the total cost of the rule will equal about $88.7 million. The present value of the total costs will equal $78.2million with a 3 percent discount rate and $66.8 million with a 7 percent discount rate. Over 10 years, the annualized present value will equal $9.2 million with a 3 percent discount rate and $9.5 million with a 7 percent discount rate.

Table 15. Summary of the Current and Present Value of the Total Costs.

Year	One-Time Costs ($ mil)	Annual Costs ($ mil)	Total Costs ($ mil)	Present Value of Total Costs ($ mil at 3 percent)	Present Value of Total Costs ($ mil at 7 percent)
1	0.4	0.3	0.7	0.7	0.6
2	0.4	0.5	0.9	0.9	0.8
3	37.8	1.4	39.2	35.9	32.0
4	17.8	3.0	20.8	18.5	15.9
5	8.6	3.8	12.4	10.7	8.8
6	0.4	3.4	3.8	3.2	2.5

7	0.4	2.4	2.8	2.3	1.8
8	0.4	2.1	2.5	2.0	1.4
9	0.4	2.2	2.6	2.0	1.4
10	0.4	2.7	3.1	2.3	1.6
Total	**66.9**	**21.8**	**88.7**	**78.2**	**66.8**

Numbers may not sum due to rounding.

D. Benefits

The final rule requires certain changes to the content of prescription drug labeling to improve the quality of this information source. To effectively communicate, labeling should be accessible, easily understood, accurate, reliable, and up-to-date. Labeling with all of these attributes provides a useful resource that can aid the decision making processes of persons prescribing drugs. The widespread adoption of electronic labeling has improved the accessibility of labeling. Health care providers obtain labeling quickly and easily from many sources, including a manufacturer's website, the Daily Med website, or from one of the many third party providers of labeling. Moreover, health care providers can easily obtain the most recent FDA-approved labeling from the Agency's Drugs@FDA website. Thus, this final rule aims to address some of the other aspects of effective communication.

Current prescription drug labeling often lacks important information used by health care providers and patients to help with decisions about the use of prescription drugs during pregnancy and lactation, and to understand the potential risks of certain prescription drugs to females and males of reproductive potential. When new drugs are initially approved, often the only information included in labeling is the pregnancy category and the reproductive toxicity data from animal studies. Over time, data on use of a drug in pregnancy accumulate and provide information that helps health care providers and patients with their treatment decisions.

For labeling subject to the PLR, information will be presented in a narrative, following a standardized order and format with clear subheadings. New subheadings within each subsection will direct health care providers to key information for pregnant and lactating women and females and males of reproductive potential. The revised "Pregnancy" subsection will include contact information for and a standard statement on pregnancy exposure registries if there is a scientifically acceptable registry, a risk summary (including a background risk statement), clinical considerations for health care providers when making prescribing decisions, and a discussion of the data underlying the risk summary and clinical considerations. Similarly, the "Lactation" subsection will include a risk summary (including a risk-benefit statement, unless breast feeding is contraindicated), a discussion of clinical considerations, and a discussion of the data underlying the risk summary and clinical considerations.

To minimize unnecessary clutter in the labeling, when certain information is unavailable the final rule allows applicants to eliminate certain subheadings, including "Pregnancy Exposure Registry" in the "Pregnancy" subsection, "Clinical Considerations" in both the "Pregnancy" and "Lactation" subsections, and "Data" in both the "Pregnancy" and "Lactation" subsections. When pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest potential drug-associated fertility effects, the final rule will require that the "Females and Males of Reproductive Potential" subsection include this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility." Finally, applicants are required to remove the pregnancy category and the required statement that describes the category, from all PLR labeling and remove the pregnancy category, but not the required statement that describes the category, from non-PLR labeling.

As discussed in the preliminary regulatory impact analysis (73 FR 30854), published studies report that the majority of women take at least one prescription drug during pregnancy and while lactating. Requiring labeling that more effectively communicates the risks and benefits of a drug during pregnancy and while lactating can help inform discussions between health care providers and their female patients of reproductive potential with chronic conditions should their patients become pregnant while taking prescription drugs. Similarly, including a statement about the benefits of breastfeeding (unless contraindicated) will help providers and patients make informed decisions about prescription drug use during lactation. Moreover, providing a background risk statement in the "Pregnancy" subsection will give context to the new risk summary. We anticipate that the sum of all of the required changes will improve the overall quality of labeling and make prescription drug labeling a more useful communication tool for health care providers.

We contracted with a private company to conduct research to provide insight into how health care providers make decisions about prescription drug use during pregnancy and lactation, and how health care providers use FDA-approved prescribing information to support their decision making. The specific objectives of this study were to understand how health care providers used FDA-approved prescribing information when making treatment decisions for pregnant and lactating women with chronic conditions, to determine the degree to which health care providers regarded prescribing information as a useful tool for their decision making, and to gain insight to help define measures that could be used to quantify the value of prescribing information as a tool for these decision makers. It should be noted that the research was not designed to test the proposed PLLR labeling or labeling in use at the time of the study, and interviewees were not asked to look at any labeling during the interviews.

This research was conducted in two phases. During the first phase, the contractor interviewed Agency and external experts to create a detailed expert model; a model that summarizes the knowledge about a topic, and depicts the detailed influences and the knowledge needed to make judgments about the topic. This expert model describes the factors that the experts hypothesized may influence health care providers' decision making regarding prescriptions for pregnant and lactating women with chronic conditions (Ref. 3).

The model also provided the framework to design the second phase of the research-- a mental models research study (Ref. 4). Researchers can identify potential alignments and gaps between the understanding of experts and interviewees by comparing the expert model and the mental model. Used often for risk communication, mental models research is an established risk analysis approach to evaluate decision making practices that requires the synthesis of complex issues. A person's mental model affects how that person defines a problem, reacts to issues, and makes decisions about a question. This approach considers not only the data available to make decisions, but also the individuals' experiences, beliefs and approaches to issues. Using structured interviews, researchers systematically reveal the set of values and beliefs that influence how individuals make certain decisions, including complex decision making processes. The interview questions developed from the expert model were designed to elicit specific responses on factors that influence decision making when treating pregnant or lactating women with chronic conditions.

For the mental models phase of the research, the contractor conducted structured, one-on-one, confidential interviews with 54 health care providers. The providers were divided into 2 cohorts. Cohort 1 included obstetricians-gynecologists, primary care physicians and nurse midwives; Cohort 2 included cardiologists, neurologists, allergists-pulmonologists and

psychiatrists. The specialties included in Cohort 2 represent specialties that would often treat pregnant and lactating women with chronic conditions; conditions that could require treatment with drugs. Nurse midwife participants were recruited from an announcement in the American College of Nurse Midwives' newsletter, and physicians were recruited from mailings to office-based physicians practicing more than 8 years in the United States based on a random sample of 5,000 physicians from the American Medical Association's Physician Masterfile.

The findings from the mental models research confirm many assumptions from the expert model on how providers used, or did not use, labeling information, including the pregnancy category system. The mental models research produced 3 key findings:

1. Treatment decisions are complex. Health care providers weigh many factors in making treatment decisions for pregnant and lactating women with chronic conditions, and often take a team-based approach to manage these decisions. Most interviewees stressed that because chronic conditions usually require treatment, it is important to find the most appropriate medication. Some factors influencing these decisions include weighing the need for treatment and risk of inadequate treatment, the risk of the drug on the fetus or newborn baby, the pregnancy category, and familiarity with the condition or drug. Factors influencing confidence in treatment decisions include their experiences with the disease being treated and comfort in treating these patients. The quality of human data, when it was available, increased the confidence of the decision making and lack of human data was viewed as a barrier to "sound decision making."
2. Health care providers seek trusted, conclusive and accessible information. Prescription labeling was not a primary source of information for decision making on drug use in pregnancy; consultation with the patient's medical team or other colleagues was the most

trusted source of information. Primary reasons cited for not using labeling included familiarity with the drug, lack of availability of the labeling at the time of decision making, poor readability or accessibility of the information; interviewees were more likely to use the PI for new or unfamiliar drugs. When interviewees consulted labeling, normally from secondary sources, the pregnancy category appeared to increase their confidence in decisions

3. Interviewees judged the quality of labeling by its availability, accessibility and clinical relevance. The majority of interviewees described the labeling format for prescribing information as inadequate. They made many important suggestions for improvement focused on simplifying the information presented, centralizing relevant information, and making any information included clinically relevant and timely.

The findings from this research affirm many concerns raised by stakeholders and experts about the pregnancy categories and their potential misuse, and the current format of prescribing information for the use of drugs during pregnancy and while breastfeeding. The final rule will address many of the opportunities to improve prescribing information that were raised by the mental models research. One goal of the PLLR is to provide more clinically relevant information about a drug to help inform the decisions of health care providers. Providing information in a narrative form and including discussions about the data underlying the risk information in the labeling may increase providers' confidence in the usefulness of the labeling information.

Until health care providers familiarize themselves with the new labeling content and format, they may spend more time reading labeling than under the current system. However, the mental models research findings suggest that health care providers now seek other sources of

information before reading the drug product labeling. Studies on the frequency that health care providers refer to labeling are dated and precede the widespread adoption of electronic information sources. Furthermore, the use of secondary sources of labeling information complicates any estimate of additional time health care providers might spend reading the new labeling content. How quickly providers of secondary information incorporate the new content and the outreach efforts these companies make to inform their users about the new content will influence how health care providers use the new content. However, from the mental models research we expect that health care providers will seek trusted, conclusive and accessible information when considering complex treatment decisions for pregnant and lactating women with chronic conditions. Consistent with consumer choice theory, we expect that health care providers will only read the new labeling content if they perceive that the benefit of the information is equal to or exceeds the cost of time they must spend to read the labeling. Although we lack information about the magnitude of this tradeoff to make a reasonable estimate of the net benefit of the labeling to health care providers, we expect there will be a positive net benefit.

The final rule completes another part of the PLR initiative to make prescription drug labeling a more effective communication tool. Whether the changes required by the final rule will encourage health care providers to use prescription drug labeling more frequently in their decision making processes is unknown. However, the Mental Models Research study showed that decisions about prescription drug use during pregnancy and lactation are complex. Our actions as a regulatory agency may not directly impact these decisions, but by addressing some of the shortcomings of labeling identified by stakeholders and experts, we can ensure the availability of better quality prescription drug labeling. How better quality information will

affect health care providers prescribing decisions and patient outcomes is uncertain and beyond the control of the Agency. Unfortunately, without a predicted change in behavior or outcomes, we are unable to quantify the benefits of the final rule.

E. Alternatives Considered

1. No New Regulatory Action

This alternative is the baseline against which we measure the costs and benefits of the other regulatory alternatives.

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 in the Labeling of All Other Approved Applications ("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 rule. The scope of this alternative would be narrower than that of the final rule. Based on our analysis for the final rule, we anticipate that 10 years after the effective date, labeling of about 800 branded drugs and labeling of about 1,200 generic drugs would contain the new content. This alternative would also require that, within 3 years of the effective date, manufacturers remove from all labeling for drugs approved before the effective date of the pregnancy labeling final rule, the pregnancy category if it exists, but not the required statement that describes the category. This requirement would affect labeling of about 2,420 branded drugs and about 5,480 generic drugs. Repackagers and relabelers would also need to change labeling of about 7,750 drugs. We estimate the present value of the total costs of this alternative over ten years would equal about $52.1 million with a 3 percent discount rate and $45.4 million with a 7 percent discount rate. The annualized costs total $6.1 million with a 3

percent discount rate and $6.5 million with a 7 percent discount rate.

Because the labeling of fewer drugs would include the new pregnancy and lactation labeling content and the new "Females and Males of Reproductive Potential" subsection, the costs of this alternative are less than the final rule. However, because fewer drugs would have labeling with the new content, the potential benefits of this alternative, although uncertain, might be less than those of the final rule. This alternative would create confusion because only some of the labeling in the PLR format would include the new pregnancy and lactation content. This would effectively create three labeling formats---non-PLR labeling, PLR labeling not subject to PLLR, and PLR labeling subject to PLLR. Such confusion would undermine the credibility of FDA-approved labeling and create a disincentive for health care providers to use the labeling.

3. Require the Labeling of All Approved Applications to Conform to the New Content Requirements

In contrast to the final rule, this alternative has the broadest scope and would require that new content be added to the labeling of an additional 2,420 branded drugs and 5,480 generic drugs. With this alternative, over 10 years, labeling of a total of 3,220 branded drugs and 6,680 generic drugs would have the new content. The implementation schedule and estimated costs for future applications and for approved applications subject to the PLR would be the same as for the final 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 prescription drug labeling, depending on the approval date. The length of time since a drug's approval determines the amount of information available for the new content. In general, more information about clinical experience is available for older drugs than for newly approved drugs. 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. To account for these potential differences in the costs for the labeling of older drugs, this analysis uses a range of costs for drugs not subject to the PLR. One-time costs to collect and organize information range from $21,200 to $24,200 for branded drugs. If the labeling of older drugs is longer than that of newly approved drugs, manufacturers of older drugs might incur higher material costs to print longer labeling. Over 10 years, the present value of the total costs ranges from $118.0 million to $121.2 million with a 3 percent discount rate and ranges from $92.7 million to $95.1 million with a 7 percent discount rate. The annualized cost of this alternative ranges from $13.8 million to $14.2 million with a 3 percent discount rate and ranges from $13.2 million to $13.5 million with a 7 percent discount rate.

4. Summary of Regulatory Options

Table 16 of this document shows the total and incremental costs of the final rule and regulatory alternatives. We expect that the total benefits of the regulatory alternatives will be directly related to the costs, because the more costly the alternative, the more drugs will 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.

Table 16. Comparison of Alternatives [1]

	Annualized Costs with 3 Percent Discount Rate ($ mil)	Annualized Costs with 7 percent Discount Rate ($ mil)	Incremental Costs with 3 Percent Discount Rate ($ mil)	Incremental Costs with 7 Percent Discount Rate ($ mil)
No new regulatory action	0	0	N/A	N/A

Content required for labeling prospectively	6.1	6.5	6.1	6.5
Final rule	9.2	9.5	3.1	3.1
Content required for labeling of all approved drugs	14.2	13.5	5.0	4.0

[1] Numbers may not sum due to rounding. 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. Only the upper bound costs are displayed with the alternative for all approved drugs.

III. Regulatory Flexibility Analysis

A. The Need for, and the Objectives of, the Final Rule

The Physician Labeling Rule left unchanged the content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of prescription drug labeling. This decision gave the Agency sufficient time to meet with experts and stakeholders to develop a regulatory framework that encourages applicants to prepare content that clearly communicates available information about drug use during pregnancy and lactation. The primary objectives of the final rule are to update the content of these subsections of prescription drug labeling, and to eliminate the pregnancy category system. Experts and stakeholders agree that the current pregnancy categories do not provide adequate information and can be misinterpreted. For example, category C, the most frequently assigned category, provides no meaningful information to aid decisions about drug use during pregnancy and lactation.

The final rule will encourage applicants to include narrative information about drugs. As part of their decision making processes, prescribers gather information from many sources including prescription drug labeling. Narrative information can convey nuances about a drug

that are lost with simple rankings or bulleted lists. The revised labeling can provide a valuable resource to clinicians faced with the complex decision about prescribing drugs to females and males of reproductive potential. Having the most current and complete information available about a drug will help clinicians and their patients understand the relative risks and benefits of prescription drug use during pregnancy and lactation.

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

The final rule will affect all small entities responsible for prescription drug labeling required to include the affected subsections. The Small Business Administration establishes thresholds for small entities by industries based on the North American Industry Classification System (NAICS). The Small business Administration considers as small Pharmaceutical Preparation Manufacturing firms (NAICS 325412) with fewer than 750 employees and Biological Product Manufacturing firms (NAICS 325414) with fewer than 500 employees. Repackagers and Relabelers, classified by the U.S. Census Bureau as Drugs and Druggists' Sundries Merchant Wholesalers (NAICS 424210) with 100 or fewer employees are considered small by SBA. The U.S. Census Bureau reports employment size data for manufacturing establishments and employment size data for wholesale firms. Based on the 2007 Economic Census, there were 350 biological product manufacturing establishments and 991 pharmaceutical preparation manufacturing establishments. Many firms included in the Drugs and Druggists' Sundries Merchant Wholesalers industry deal with products not affected by the final rule such as vitamins and supplements. To narrow our analysis to the subsector of the industry most likely affected, we used 2007 Economic Census data for General-line drugs merchant wholesalers (NAICS 4242101) for repackagers and relabelers. Census data reports that 3,014 firms operated for the entire year as general-line drugs merchant wholesalers. The vast majority of

manufacturing establishments and drug wholesale firms fall below the SBA size standard for small entities. Table 17 shows that small establishments account for 96 percent of the biological product manufacturing establishments and table 18 shows that small firms account for 96 percent of drug wholesale firms.

Table 17. Biological Product Manufacturing Establishments by Employment Size

	0-9 Employees	10-19 Employees	20-99 Employees	100-500 Employees	Small Establishments	All Establishments
Number of Establishments	114	40	130	51	335	350
Total Value of Shipments ($ mil)	N.A.	N.A.	1,388.9	5,523.5	6,912.4	21,798.3
Average Value of Shipments ($ mil)	N.A.	N.A.	10.7	108.3	20.6	62.3
Share of Establishments	33%	11%	37%	15%	96%	100%

Source: U.S. Census Bureau, 2007 Economic Census, "EC0731SG3: Manufacturing: Summary Series: General Summary: Industry Statistics for Subsectors and Industries by Employment Size: 2007."

Table 18. Drugs and Druggists' Sundries Merchant Wholesaler Firms by Employment Size

	0-9 Employees	10-19 Employees	20-99 Employees	Small Firms	All Firms
Number of Firms	1,994	451	439	2,884	3,014
Sales ($ billion)	3.6	3.1	13.9	20.6	253.1
Average Sales ($ mil)	1.8	6.8	31.7	7.1	84.0
Share of All Firms	66%	15%	15%	96%	100%

Source: U.S. Census Bureau, 2007 Economic Census, "EC0742SSSZ5: Wholesale Trade: Subject Series - Establishment and Firm Size: Summary Statistics by Employment Size of Firms for the United States: 2007."

Census employment size classes for pharmaceutical preparation manufacturing do not correspond to SBA size categories. For this analysis, we use the mid-point of the 500 to 999

employee size to estimate small establishments with 500 to 749 employees. The Census data suggest that approximately 95 percent of pharmaceutical preparation manufacturing establishments are small entities as shown in table 19. Despite the large number of small entities, foreign or large companies manufacture over 80 percent of the prescription drugs.

Table 19. Pharmaceutical Preparation Manufacturing Establishments by Employment Size

	0-9 Employees	10-19 Employees	20-99 Employees	100-749 Employees	Small Establishments	All Establishments
Number of Establishments	408	77	249	209	943	991
Total Value of Shipments ($ mil)	584.7	429.2	9,899.3	61,958.1	72,871.3	142,876.3
Average Value of Shipments ($ mil)	1.4	5.6	39.8	297.2	77.3	144.2
Share of All Establishments	41%	8%	25%	21%	95%	100%

Source: U.S. Census Bureau, 2007 Economic Census, "EC0731SG3: Manufacturing: Summary Series: General Summary: Industry Statistics for Subsectors and Industries by Employment Size: 2007."

Based on our analysis of labeling submitted to the Agency, we tallied the number of unique versions of labeling. Breaking down our counts by establishment size, we estimated that about 180 small drug manufacturers will be affected by the final rule, including 60 generic drug manufacturers, 100 branded drug manufacturers, and 20 manufacturers of both branded and generic drugs. Using these findings, we calculate the average number of revisions for existing branded drug labeling by the year when the manufacturer must revise the labeling. Although as shown in table 20 the average number of revisions for each manufacturer will be modest, 2 small manufacturers with 9 or fewer employees will need to change the content of labeling for 2 or 3 branded drugs in a single year.

Table 20. Average Number of Existing Labeling Revisions by Branded Drug Manufacturers

	Average Number of Labeling Revisions to Remove Category Letter in Year 3	Average Number of Content Revisions in Year 3	Average Number of Content Revisions in Year 4	Average Number of Content Revisions in Year 5
0-9 Employees	1	0	1	0
10-19 Employees	2	1	0	0
20-99 Employees	2	0	1	0
100-750 Employees	3	0	1	0

Using the data from our analysis of submitted labeling, we calculate the average number of revisions for generic drug manufacturers based on when and how the rule affects the labeling of the reference listed drug. Table 21 shows the average number of labeling revisions for existing generic drugs. Regardless of size, generic drug manufacturers will make more revisions to remove the pregnancy category than branded drug manufacturers. On average, however, generic drug manufacturers with fewer than 20 employees will not need to revise any existing labeling to add the new required content.

Table 21. Average Number of Existing Labeling Revisions by Generic Drug Manufacturers

	Average Number of Labeling Revisions to Remove Category Letter in Year 3	Average Number of Content Revisions in Year 3	Average Number of Content Revisions in Year 4	Average Number of Content Revisions in Year 5
0-9 Employees	3	0	0	0
10-19 Employees	3	0	0	0
20-99 Employees	2	1	1	0
100-750 Employees	4	1	0	1

Similar to manufacturers, we use data on submitted labeling to estimate the number of repackagers and relabelers that would need to revise labeling. We find that about 34 small or privately held wholesale firms that repackage or relabel prescription drugs will revise existing labeling; 17 of these firms need to remove the pregnancy category, but not the required statement

describing the category, in year 3. Because repackagers and relabelers will spend the same level of effort to add new content or to remove the pregnancy category, the average numbers for year 3 include both actions. Table 22 shows that repackagers and relabelers will make substantially more revisions than manufacturers. As stated previously, these firms may frequently change the manufacturers that supply their drugs for non-regulatory reasons. We lack information to refine this estimate, but note that our estimate likely includes labeling for drugs that repackagers and relabelers may no longer market. Because we find there is a wide range of affected drug labeling for all years and all size of firms, in table 22 we present the range of affected labeling.

Table 22. Average Number of Existing Labeling Revisions by Repackagers and Relabelers

	Average Number of Labeling Revisions in Year 3	Range of Labeling Revisions in Year 3	Average Number of Labeling Revisions in Year 4	Range of Labeling Revisions in Year 4	Average Number of Labeling Revisions in Year 5	Range of Labeling Revisions in Year 5
0-9 Employees	43	1 to 156	8	0 to 36	4	0 to 19
10-19 Employees	82	1 to 245	14	0 to 33	8	0 to 26
20-99 Employees	159	1 to 794	25	0 to 134	15	0 to 84

C. Burden on Small Entities

In our initial analysis, we asked for comment from small entities about the possible impact that the rule might have, especially in year 3 when a large number of labeling revisions will be needed. We received no comments from industry and thus assume that our initial analysis was a reasonable estimate of the burden on small entities. For our final analysis, we update our counts of affected labeling and add repackagers and relabelers to the analysis.

We find that only 5 biological product manufacturers are small according to the SBA size standards. Because Census data does not include the value of shipments for these firms, we group them together with the pharmaceutical preparation manufacturers to estimate the burden of

the final rule. Because the costs vary by the type of action, we separate the costs to remove the pregnancy category, but not the required statement, in year 3, from the costs to collect and organize the new content, and to revise existing labeling to add the new content in years 3, 4 and 5. Table 23 shows the average costs per establishment for these small manufacturers..

Table 23. Average Costs Per Establishment by Size for Branded Drug Manufacturers

	Average Cost to Remove Category Letter ($)	Average Cost of Labeling Revisions in Year 3 ($)	Average Cost of Labeling Revisions in Year 4 ($)	Average Cost of Labeling Revisions in Year 5 ($)
0-9 Employees	3,580	4,790	13,560	3,990
10-19 Employees	4,920	11,700	5,850	5,850
20-99 Employees	8,390	830	18,210	4,140
100-750 Employees	16,270	7,940	18,870	8,440

As shown in table 24, generic drug manufacturers will incur lower average costs for PLR-labeling than equivalent-sized branded drug manufacturers. In contrast, generic drug manufacturers with fewer than 20 employees will incur higher average costs for non-PLR labeling than equivalent-sized branded drug manufacturers.

Table 24. Average Costs Per Establishment by Size of Generic Drug Manufacturers

	Average Cost to Remove Category Letter ($)	Average Cost of Labeling Revisions in Year 3 ($)	Average Cost of Labeling Revisions in Year 4 ($)	Average Cost of Labeling Revisions in Year 5 ($)
0-9 Employees	10,390	430	580	1,010
10-19 Employees	8,160	470	700	930
20-99 Employees	4,850	1,670	1,670	1,210
100-750 Employees	12,120	2,530	1,070	2,460

As explained previously, the costs for repackagers and relabelers to revise labeling are the same for all firm sizes and types of labeling revisions. Table 25 shows the average per firm costs for years 3, 4 and 5. These per firm costs for small repackagers and relabelers exceed those for small manufacturers in all years for all size of firms.

Table 25. Average Costs per Firm by Size of Repackager and Relabeler

	Average Cost of Labeling Revisions in Year 3 ($)	Average Cost of Labeling Revisions in Year 4 ($)	Average Cost of Labeling Revisions in Year 5 ($)
0-9 Employees	57,024	10,720	4,764
10-19 Employees	109,497	18,377	10,529
20-99 Employees	213,358	33,574	20,547

We use the average value of shipments from table 19 to estimate the burden on manufacturers, and the average value of sales from table 18 for drug wholesalers to estimate the burden on repackagers and relabelers. Table 26 shows the average burden on small branded drug manufacturers and table 27 shows the average burden on small generic drug manufacturers. Based on averages, the final rule will not create a significant burden on small manufacturers. It should be noted, however, that data for all small branded drug manufacturers with fewer than 10 employees suggests that the burden for these individual establishments may exceed 1 percent in any single year; in year 4, the burden may equal about 3.8 percent of the total value of shipments for one manufacturer and in year 5 the burden may equal about 2.5 percent of the total value of shipments for another manufacturer. On average, small generic drug manufacturers face a similar burden to small branded drug manufacturers. For generic drug manufacturers with fewer than 10 employees, individual data suggests that the burden to remove the category letter in year 3 will exceed 1 percent of the total value of shipments for 4 establishments, with the burden for these manufacturers ranging from 1.5 percent to 5.0 percent.

Table 26. Average Burden Per Establishment on Small Branded Drug Manufacturers

	Average Cost to Remove Category Letter as a Share of	Average Cost as a Share of Average Value of Shipments	Average Cost as a Share of Average Value of Shipments	Average Cost as a Share of Average Value of Shipments

	Average Value of Shipments	(Year 3)	(Year 4)	(Year 5)
0-9 Employees	0.2%	0.3%	1.0%	0.3%
10-19 Employees	0.1%	0.2%	0.1%	0.1%
20-99 Employees	0.0%	0.0%	0.0%	0.0%
100-750 Employees	0.0%	0.0%	0.0%	0.0%

Table 27. Average Burden Per Establishment on Small Generic Drug Manufacturers

	Average Cost to Remove Category Letter as a Share of Average Value of Shipments	Average Cost as a Share of Average Value of Shipments (Year 3)	Average Cost as a Share of Average Value of Shipments (Year 4)	Average Cost as a Share of Average Value of Shipments (Year 5)
0-9 Employees	0.7%	0.0%	0.0%	0.1%
10-19 Employees	0.1%	0.0%	0.0%	0.0%
20-99 Employees	0.0%	0.0%	0.0%	0.0%
100-750 Employees	0.0%	0.0%	0.0%	0.0%

The burden for small repackagers and relabelers appears to be more pronounced than for small manufacturers. Driven by a large number of labeling revisions to remove the pregnancy category, but not the statement that describes the category, the average burden as a share of average sales will exceed 1 percent for firms with fewer than 20 employees in year 3 (table 28). Furthermore, the data on the number of revisions for individual firms in year 3 suggests that the burden for 3 firms with fewer than 10 people will range from 6.3 percent to 11.6 percent; the burden for 4 firms with 10 to 19 employees will range from 1.4 percent to 4.8 percent. In addition, the burden for the same 3 individual firms with fewer than 10 employees will exceed 1 percent in year 4 and the burden for 1 of these firms with fewer than 10 employees will exceed 1 percent in year 5. Although the average burden for larger firms does not exceed 1 percent in any year, we have identified 5 firms with 20 to 99 employees where the burden is expected to exceed the average burden, and will range from 1.4 percent to 3.4 percent.

Table 28. Average Burden Per Establishment on Small Repackagers and Relabelers

	Average Cost as a Share of Average Sales (Year 3)	Average Cost as a Share of Average Sales (Year 4)	Average Cost as a Share of Average Sales (Year 5)
0-9 Employees	3.2%	0.6%	0.3%
10-19 Employees	1.6%	0.3%	0.2%
20-99 Employees	0.7%	0.1%	0.1%

Based on our analysis of current data, the final rule will likely have a significant impact on a substantial number of small entities, especially repackagers and relabelers. Consequently, we decline to certify the final rule.

D. Description of Special Skills and Recordkeeping

The compliance requirements for small entities under the rule are the same as those described above for other affected entities. Applicants, manufacturers and persons responsible for the content of labeling have the skills needed to collect and organize the new information required by the final rule and to code the labeling in SPL. Changing prescription drug labeling to accommodate new information or revise existing information is standard practice for applicants and manufacturers. Repackagers, relabelers, and manufacturers currently submit labeling in SPL to the Agency. Because the final rule requires no actions beyond those tasks performed currently, no additional skills will be needed.

For changes in the content, applicants or manufacturers of branded drugs will submit a labeling supplement and obtain prior approval from the Agency. Applicants or manufacturers of generic drug products, repackagers and relabelers will need to submit labeling to the Agency, but need not obtain prior approval because they will duplicate the information approved for the reference listed drug labeling. Manufacturers will keep records of their supplements and submissions to the Agency. Because these are electronic documents, the time to maintain these

records is minimal and included in the overall costs of modifying the content of labeling and revising the prescription drug labeling.

IV References

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