DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. FDA–1977–N–0013] (formerly Docket No. 1977N–0094L)

RIN 0910–AF36

Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph; Corrections

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule, corrections.

SUMMARY: The Food and Drug Administration (FDA) is correcting a final rule that appeared in the **Federal Register** of April 29, 2009. The document requires important new organ-specific warnings and related labeling for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products. The new labeling informs consumers about the risk of liver injury when using acetaminophen and the risk of stomach bleeding when using nonsteroidal anti-inflammatory drugs (NSAIDs). The document was published with an incorrect Analysis of Impacts section and omitted a reference from the reference section of the final rule. The document was also published with an error in the codified text regarding the introductory sentence to the stomach bleeding warning for NSAIDs. This document replaces the incorrect Analysis of Impacts section with the correct Analysis of Impacts section, adds a reference to the reference section of the final rule, and corrects the codified text.

DATES: *Effective Date*: This final rule is effective April 29, 2010.

Compliance Date: The compliance date for all products subject to this final rule, including products with annual sales less than $25,000, is April 29, 2010.

FOR FURTHER INFORMATION CONTACT: Arlene Solbeck, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, 301–796–2090.

SUPPLEMENTARY INFORMATION: In FR Doc. E9–9684, published on April 29, 2009 (74 FR 19385), make the following corrections:

1. Beginning on page 19401 and ending on page 19406, replace section VI. Analysis of Impacts with the following text:

VI. Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. 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 $130 million, using the most current (2007) Implicit Price Deflator for the Gross Domestic Product. We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

We conclude that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As discussed in this section, we have determined that this final rule will not have a significant economic impact on a substantial number of small entities, but we lack sufficient information on the distribution of the burden to certify that it is not significant.

The impact on industry, in terms of costs of compliance, are presented in section VI.B of this document and summarized in table 2 of this document. The societal costs and benefits of this final rule are summarized in table 3 of section VI.B of this document.

A. Need for the Rule

In 2002, an FDA Advisory Committee recommended changes to the labeling of OTC acetaminophen and NSAID drug products to better inform consumers about the active ingredients and possible side effects caused by improper use. Current labels provide inadequate information about the risk of improper use. Although we consider acetaminophen to be safe and effective when labeled and used correctly, using too much can lead to liver injury and death. Similarly, the use of NSAIDs can lead to stomach bleeding and kidney damage. The number of cases of injury reported is a very low percentage of the total use of OTC acetaminophen and NSAID drug products. For many people, the risks are quite low because they use these products only occasionally. The risks may be greater for people who use these products more frequently and/or do not follow the labeling information on the package. The risk of injury may be increased for certain populations and under certain conditions of use.

There are multiple reasons for unintentional acetaminophen overdoses. First, acetaminophen is an active ingredient in a wide variety of both OTC and prescription drug products. For prescription products, the immediate container may not state that the product contains acetaminophen or state the maximum daily dose limit. Consumers may often fail to recognize the presence and amount of acetaminophen ingredients in OTC and prescription drug products. This lack of knowledge can result in a person using two different products containing acetaminophen simultaneously. Moreover, many consumers are unaware that exceeding the recommended dosage for acetaminophen can lead to unintentional overdosing and cause potential harm. Based on the evidence discussed in this document, we find that there is sufficient incidence of liver injury associated with acetaminophen to warrant new labeling, and that without the new labeling, acetaminophen products would no longer be considered generally recognized as safe and effective and not misbranded for OTC use.

Results of several large-scale clinical studies performed in the United States and in other countries have established that the use of NSAIDs is an important risk factor for serious stomach adverse events, especially bleeding. The risk is higher for certain populations. Based on the evidence discussed in this document, we further find that NSAIDs increase the risk for stomach adverse events and that, without a new stomach bleeding warning in the labeling for NSAIDs, the products would no longer be considered generally recognized as safe and effective and not misbranded for OTC use.

The purpose of this final rule is to amend our OTC drug labeling regulations to include new warnings and other labeling requirements to advise consumers of potential risks and when to consult a doctor (see table 1 in section II.B.2 of this document). We are also removing the alcohol warning in § 201.322 and incorporating new alcohol-related warnings and other labeling for all OTC acetaminophen and NSAID drug products. We are requiring certain warning information targeted to age-specific populations. In addition, we are requiring that the presence of acetaminophen or any NSAID would appear prominently on a product's principal display panel (PDP). Without this final rule, the labeling of these products will not provide sufficient warnings of risks to consumers.

B. Impact of the Rule

We contracted Eastern Research Group, Inc. (ERG) to assess the costs and benefits of the proposed rule on which this final rule is based. The full ERG report (Ref. 56), including details on methods, assumptions, cost calculations, and findings, is on file in the Division of Dockets Management (71 FR

77314 at 77341). The most significant change from the proposal is the requirement that warning statements appear on both the outer container and on the immediate container. We, therefore, contracted with ERG to perform an updated store survey and analysis to assess the costs of the changes in this final rule. ERG's 2008 ''Addendum to the Cost Benefit Analysis: Final Internal Analgesic, Antipyretic, and Antirheumatic Drug Products Rulemaking'' (Ref. 57) is also on file with the Division of Dockets Management. Most of ERG's methods, assumptions and analysis used for the proposed rule remain unchanged for this final rule. The following is a summary of ERG's findings.

1. Cost of Compliance

Manufacturers and marketers of OTC acetaminophen and NSAID drug products would incur one-time costs to revise affected product labeling to comply with this rule. We estimated costs for a major labeling revision using a pharmaceutical labeling revision cost model. We used an implementation period of 12 months. The labeling model is described in detail in Appendix A of the ERG report cited in the 2006 proposed rule.

To develop the original model, we and ERG interviewed pharmaceutical representatives from regulatory, legal, manufacturing controls, and labeling departments to collect information on labeling change cost components, type of personnel affected, and costs. The model incorporates data on average industry costs by company size, including, where applicable, modifications to packaging configurations. Industry consultants also provided information on model inputs related to the OTC acetaminophen and NSAID drug product industry, the labeling revision process, the costs of modifying labeling, and the frequency of packaging reconfiguration changes.

The baseline for this final rule is full compliance with the format and content requirements for OTC drug product labeling in 21 CFR 201.66 established in a 1999 final rule (64 FR 13254, March 17, 1999). In the 1999 final rule, we accounted for the total incremental costs to comply with the format and content requirements, including using a 6 point font size and related costs for increased package size and longer labeling where applicable. We note that, although some forms of packaging (for small quantities) have been granted extensions on compliance dates, many packaging alternatives now exist that can accommodate the format and content requirements.

Manufacturers routinely redesign labels at varying intervals and have standardized procedures in place for complying with our requirements. Based on consultant input, manufacturers of OTC acetaminophen and NSAID drug products typically redesign one-half of their labels every 2 years, the remainder every 3 years. The costs of labeling change depend on the type of labeling (e.g., carton and container label) and whether there is sufficient labeling space to accommodate the proposed changes.

There are an estimated 22,500 OTC acetaminophen and NSAID drug product stock keeping units (SKUs), split evenly among branded and private labels, according to an industry consultant.[9] We assume that branded SKUs are distributed as follows by firm size: 50 percent small, 17 percent medium, and 33 percent large. Based on ERG's store survey, roughly 98 percent of OTC acetaminophen and NSAID drug products were packaged in containers within cartons and 2 percent in containers without outer cartons. About 5 percent of the 98 percent of products packaged in cartons contained blister packs. For the final rule, ERG revised the distribution of SKUs among OTC acetaminophen and NSAID drug products as follows: Acetaminophen, 32 percent; NSAIDs except ibuprofen, 32 percent; ibuprofen, 34 percent; and combinations of acetaminophen and NSAIDs, 2 percent.[10]

To assess the increase in label space and package size requirements, ERG purchased a variety of OTC IAAA packaging arrangements. ERG then determined the current baseline warning language and evaluated spacing constraints on packaging. Consistent with findings discussed in the proposed rule, ERG concluded that all current packaging except blister packs can accommodate the required changes in this final rule without altering label sizes, package sizes, or adding nonstandard labels. For blister packages, all outer cartons were judged to have adequate label space available. With respect to the immediate container, blister packs for OTC acetaminophen were judged able to accommodate warning statements, but the OTC NSAID blister packs could not. Therefore, ERG estimated that for OTC NSAIDs, both the inner blister pack container and the outer carton would need to be expanded. This assumption allows for the same number of unit doses per card and a larger carton to accommodate the larger cards.

Table 2 of this document presents the estimated total one-time and recurring annual costs of compliance with this final rule in 2002 dollars. The total estimated first-year one-time costs to revise labeling are $62.7 million. Recurring costs are $1.5 million per year. The increases in cost from the proposed rule are driven by the increased percentage of OTC ibuprofen SKUs, the doubling of packaging changes needed due to the final regulation, and the need to change package sizes for OTC NSAID blister packs.

TABLE 2.—ESTIMATED TOTAL ONE-TIME AND RECURRING ANNUAL COSTS OF COMPLIANCE WITH THIS RULE (IN 2002 DOLLARS)

Company Type	Product Type				
	Acetaminophen	Ibuprofen	NSAIDs Except Ibuprofen	Combinations of Acetaminophen and NSAIDs	Total
Total one-time costs (expressed as millions of dollars)					
Small brand	$2.2	$4.2	$4.0	$0.2	$10.7
Medium brand	$2.2	$3.1	$2.9	$0.2	$8.4
Large brand	$6.1	$8.5	$8.0	$0.5	$23.0
Private label	$4.5	$8.0	$7.5	$0.5	$20.5
Total	$15.0	$23.8	$22.4	$1.4	$62.7
Total recurring costs (expressed as millions of dollars)					
Small brand	$0.000	$0.089	$0.050	$0.005	$0.145

[9] Estimates of affected SKUs are 18,000 by FDA and 20,000 to 25,000 by industry consultant. This number of SKUs includes products marketed by manufacturers, repackers, relabelers, and distributors.

[10] ERG conducted a sensitivity analysis using the same distribution of products at proposal and found that costs would have been about 3 percent lower. The former distribution was: Acetaminophen, 45 percent; NSAIDs except ibuprofen, 38 percent; ibuprofen, 15 percent; and combinations of acetaminophen and NSAIDs, 2 percent.

TABLE 2.—ESTIMATED TOTAL ONE-TIME AND RECURRING ANNUAL COSTS OF COMPLIANCE WITH THIS RULE (IN 2002 DOLLARS)—Continued

Company Type	Product Type				
	Acetaminophen	Ibuprofen	NSAIDs Except Ibuprofen	Combinations of Acetaminophen and NSAIDs	Total
Medium brand	$0.000	$0.065	$0.037	$0.004	$0.106
Large brand	$0.000	$0.467	$0.264	$0.026	$0.756
Private label	$0.000	$0.290	$0.164	$0.016	$0.470
Total	$0.000	$0.911	$0.515	$0.050	$1.476

2. Alternatives

We considered and rejected the following alternatives: (1) Not adding the new information to OTC acetaminophen and NSAID drug product labeling and (2) a longer implementation period. We do not consider either of these approaches acceptable because they do not ensure that consumers will have the most current labeling information needed for the safe and effective use of these products. We consider this final rule the least burdensome alternative that meets the public health objectives of this rule.

3. Benefits

Our final rule requirements are intended to enhance consumer awareness and knowledge of the active ingredient in OTC acetaminophen and NSAID drug products. These new warnings include:

- New label warnings
- Age-specific information
- Advising consumers of potential risks and when to consult a doctor
- Prominent display of active ingredients on the PDP

The revised alcohol statements are intended to provide clearer warnings to high-risk individuals about product use. The overall intent of these requirements is to reduce the liver injury and stomach bleeding episodes that occur due to unintentional overdosing with these drugs. The requirements are also intended to reduce the incidence of adverse health outcomes among high-risk subpopulations consuming proper doses of OTC acetaminophen and NSAID drug products (e.g., people with liver disease or people prone to stomach bleeding).

Our estimate of the potential benefits of this final rule remains unchanged from the estimate discussed in the proposed rule. We estimated benefits assuming a reduction of from 1 percent to 3 percent in unintentional overdosing with OTC acetaminophen and NSAID drug products. Reducing the number of unintentional overdoses with OTC acetaminophen and NSAID drug products would reduce the number of emergency room visits, hospitalizations, and deaths attributable to these unintentional overdoses. The monetary value of these avoided adverse events, in 2007 dollars, is shown in table 3 of this document.

4. Benefit-Cost Comparison

Table 3 of this document summarizes the present value over 10 years of the compliance costs and the benefits of a 1 percent and 3 percent reduction in deaths and hospitalizations using discount rates of 7 and 3 percent. We converted ERG's present value comparison of costs and benefits to 2007 dollars using the Gross Domestic Product index of 1.0948 relative to 2001. The low end of the benefits range uses an estimate of $5 million as the value of a statistical life and includes savings from reduced hospitalizations. The high end of the benefits range uses an updated value of $7 million per statistical life and does not include savings from reduced hospitalizations. The costs of this final rule exceed the benefits using the most conservative assumption of benefits. The benefits exceed the costs of this rule at the mid to upper end of the benefits range. Comparing the present value of costs and benefits over 10 years, in 2007 dollars, costs would exceed benefits if this rule reduced deaths and hospitalizations by 2 percent or more.

TABLE 3.—PRESENT VALUE AND ANNUALIZED PRESENT VALUE OF COMPLIANCE COSTS AND POTENTIAL BENEFITS OVER 10 YEARS (IN 2007 DOLLARS)

Discount Rate	Present Value (millions of dollars)		Annualized Present Value Over 10 Years (millions of dollars)	
	Costs[1]	Benefits[2]	Costs	Benefits[2]
7 percent	$77.8	$45.1 - $172.8	$11.1	$6.4 - $24.6
3 percent	$79.8	$53.8 - $202.0	$9.4	$6.3 - $23.7

[1] The present value of compliance costs over 10 years in 2001 dollars equals $71.0 million at 7 percent and $72.9 million at 3 percent.
[2] Assumes that this final rule would reduce adverse events by 1 to 3 percent.

5. Break-Even Analysis

We note that we lack the data needed to confidently predict a percent reduction in serious cases related to unintentional overdosing. Because of the uncertainty in these estimates, we estimated an annual average number of adverse events that would need to be avoided over a 10 year period to reach a break-even point (i.e., the present value of the cost of compliance divided by the present value of the monetary value of avoiding an adverse event each year for 10 years). The following calculations are based on 2001 dollars, which will not affect the estimated break-even values to be calculated. For benefits to equal costs, this final rule would need to prevent about 2 deaths each year over 10 years [1.9 deaths ($71.0 million/$37.6 million at a 7 percent discount rate) and 1.7 deaths ($72.9 million/$43.9 million at a 3 percent discount rate)]. This estimate of deaths avoided is based on a value of $5 million per statistical life. Alternatively, if no deaths are avoided, the final rule would need to prevent about 1,058 hospitalizations each year over the 10-year period at the 7 percent discount rate ($71.0 million/$67,156), and 928 hospitalizations a year at the 3 percent discount rate ($72.9 million/$78,513). This estimate of hospitalizations avoided is based on the lowest monetized value of a poisoning episode requiring hospitalization: $8,936 per episode over 10 years at a 7 percent discount rate.

Although we lack evidence to predict with certainty a specific level of reduction in adverse events, if we assume only a 2 percent reduction in the illnesses and deaths analyzed, the benefits of this final rule

outweigh the costs. We find that this final rule will enhance public health and promote the safer use of OTC acetaminophen and NSAID drug products.

6. Final Regulatory Flexibility Analysis

This economic analysis, together with other relevant sections of this document, serves as our final regulatory flexibility analysis, as required under the Regulatory Flexibility Act. For our preliminary regulatory flexibility analysis, we calculated the average annualized compliance costs for firms in each size category and determined that the average annualized compliance costs totaled less than 1 percent of average receipts for all firm sizes. In 2007 dollars, the estimated annualized present value cost per SKU is $492 (i.e., $11.1 million divided by 22,500 SKUs) using a 7 percent discount rate over 10 years, and $416 per SKU ($9.4 million divided by 22,500 SKUs) using a 3 percent discount rate over 10 years. For private label SKUs only, the annualized present value cost per SKU is $321 ($3.6 million divided by 11,250 SKUs) using a 7 percent discount rate over 10 years, or $271 per private label SKU ($3.0 divided by 11,250 SKUs) using a 3 percent discount rate over 10 years. Similar to the proposed rule, the average annualized compliance costs of the final rule remain under 1 percent of average receipts for all firm sizes. Therefore, we tentatively conclude that this final rule will not have a significant economic impact on a substantial number of small entities.

2. On page 19407, in the second column, add the following reference:

57. Eastern Research Group, Inc., ''Addendum to the Cost Benefit Analysis: Final Internal Analgesic, Antipyretic and Antirheumatic Drug Products Rulemaking,'' Final Report, July 30, 2008.

§ 201.326 [Corrected]

■ 3. On page 19408, in the third column, correct the first sentence in § 201.326(a)(2)(iii)(A) to read as follows: ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding.''

■ 4. On page 19409, in the first column, correct the first sentence in § 201.326(a)(2)(iv)(A)(*1*) to read as follows: ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding.''

■ 5. On page 19409, in the second column, correct the first sentence in § 201.326(a)(2)(v)(A) to read as follows: ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding.''

Dated: June 23, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E9–15403 Filed 6–29–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 117

[USCG–2008–1216]

RIN 1625–AA09

Drawbridge Operation Regulations; Potomac River, Between MD and VA

AGENCY: Coast Guard, DHS.

ACTION: Final rule.

SUMMARY: The Coast Guard is changing the drawbridge operation regulations of the new Woodrow Wilson Memorial (I–95) Bridge, mile 103.8, across the Potomac River between Alexandria, VA and Oxon Hill, MD. This rule is being made in an effort to minimize the potential for major regional vehicular traffic impacts and consequences during bridge openings of the draw span while still providing for reasonable needs of marine traffic.

DATES: This rule is effective July 30, 2009.

ADDRESSES: Comments and related materials received from the public, as well as documents mentioned in this preamble as being available in the docket, are part of docket USCG–2008–1216 and are available online at *http://www.regulations.gov.* This material is also available for inspection or copying at two locations: The Docket Management Facility (M–30), U.S. Department of Transportation, West Building Ground Floor, Room W12–140, 1200 New Jersey Avenue, SE., Washington, DC 20590, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays, and the Commander (dpb), Fifth Coast Guard District, Federal Building, 1st Floor, 431 Crawford Street, Portsmouth, VA 23704–5004 between 8 a.m. and 4 p.m., Monday through Friday, except Federal holidays.

FOR FURTHER INFORMATION CONTACT: If you have questions on this rule, call Waverly W. Gregory, Jr., Bridge Administrator, Fifth Coast Guard District, at 757–398–6222. If you have questions on viewing or submitting material to the docket, call Renee V. Wright, Program Manager, Docket Operations, telephone 202–366–9826.

SUPPLEMENTARY INFORMATION:

Regulatory Information

On February 9, 2009, we published a notice of proposed rulemaking (NPRM) entitled, ''Drawbridge Operation Regulations; Potomac River, Between MD and VA'' (74 FR 6359). We received no comments on the published NPRM. No public meeting was requested, and none was held.

Background and Purpose

On July 2, 2008, we published a temporary regulation entitled ''Drawbridge Operation Regulations; Potomac River, Between MD and VA,'' in the **Federal Register** (73 FR 37806). While construction continued, the temporary rule allowed the drawbridge to remain closed-to-navigation each day from 10 a.m. to 2 p.m. until and including March 1, 2009.

The MD State Highway Administration and the VA Department of Transportation, co-owners of the drawbridge, requested to permanently maintain the Woodrow Wilson Bridge in the closed-to-navigation position each day from 10 a.m. to 2 p.m. This request was made in an effort to minimize the potential for major regional vehicular traffic impacts and consequences during bridge openings.

In reaching our decision to implement this request, we balanced the large volume of vehicular traffic moving across the bridge against the lack of large commercial vessel traffic seeking to use the bridge during this period. The Woodrow Wilson Bridge is part of the Capital Beltway Interstate Highway System. It is a critical component of that system for both local and regional traffic moving into, around, and through the Washington, DC metro area. Bridge openings cause significant traffic delays.

From a river-user standpoint, the coordinators for the construction of the new Woodrow Wilson Bridge Project have received no requests from boaters or mariners to open the bridge during the 10 a.m. to 2 p.m. timeframe since the first temporary deviation was issued in late June 2006. In fact, no requests have been received for an opening of the new bridge at all since July 3, 2006. Finally, the coordinators have received no complaints on the 10 a.m. to 2 p.m. restriction. This rule will affect only vessels with mast heights of 75 feet or greater. Furthermore, all operators of affected vessels with mast heights greater than 75 feet will be able to request an opening of the drawbridge in the ''off-peak'' vehicle traffic hours (evening and overnight) in accordance with 33 CFR 117.255(a). As discussed in the Notice of Proposed Rulemaking, currently, 33 CFR 117.255(a)(2)(i) states (paraphrasing) that the drawbridge need not open for the passage of a commercial vessel, Monday through Friday, 5 a.m. to 10 a.m. and 2 p.m. to 8 p.m. This final rule connects the two time periods by extending the operating