

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

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Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

FDA has examined the impacts of the proposed 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 proposed rule would not be an economically significant regulatory action as defined by Executive Order 12866.

If a rule has a significant economic impact on a substantial number of small businesses, the Regulatory Flexibility Act requires Agencies to analyze regulatory alternatives that would minimize any significant impact of a rule on small entities. FDA has determined that this proposed rule would 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 (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

The proposed rule would amend the current regulations on submission of changes being effected (CBE-0) supplements for safety-related labeling changes to permit abbreviated new drug application (ANDA) holders to distribute revised product labeling that differs from the labeling of its reference listed drug upon submission to FDA of a CBE-0 supplement. The proposed rule would also allow changes to the Highlights of Prescribing Information (Highlights) of drug labeling in the “Physician Labeling Rule” (PLR) format through a CBE-0 supplement. In addition, the proposed rule would establish a Web page where FDA would post information on pending CBE-0 supplements submitted for safety-related labeling changes.

The public health benefits from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing healthcare providers and the public could be improved. The proposed rule may reduce the time in which ANDA holders make safety-related labeling changes for generic drugs for which approval of the NDA for the reference listed drug has been withdrawn. In addition, the proposed rule generally would reduce the time in which all ANDA holders make safety-

Table 1 – Summary of Costs

		<u>Low Estimate</u>	<u>High Estimate</u>
Annual Net Social Costs		\$4,237	\$25,852
20-Year Present Value of	<u>3% Discount Rate</u>	\$63,040	\$384,616
Discounted Social Costs	<u>7% Discount Rate</u>	\$44,890	\$273,879

related labeling changes, by requiring such ANDA holders to submit conforming labeling changes within 30 days of FDA’s posting of the approval letter for the reference listed drug’s labeling change on its Web site. The primary estimate of the costs of the proposed rule includes costs to ANDA and NDA holders for submitting and reviewing CBE-0 supplements. We assume that the proposed rule will have no effect on the number of CBE-0 supplements submitted by biologics license application (BLA) holders.

The proposed rule is expected to generate little cost. The Agency estimates the net annual social costs to be between \$4,237 and \$25,852. The present discounted value over 20 years would be in the range of \$63,040 to \$384,616 at a 3 percent discount rate and in the range of \$44,890 to \$273,879 at a 7 percent discount rate. The net annual costs to society are summarized in Table 1.

II. Preliminary Regulatory Impact Analysis

A. Background

The labeling for approved drugs and biological products (collectively “drugs”) provide healthcare professionals and patients with information needed for the safe and effective use of the product. Application holders must promptly review all adverse drug experience information obtained or otherwise received from any source regarding their product and comply with FDA reporting and recordkeeping requirements. If changes to the labeling of an application holder’s product are needed for safety-related reasons or to otherwise ensure that labeling is accurate and up-to-date, the application holder should take the necessary steps to change the labeling. Most changes require the application holder to submit a prior approval supplement before the product can be distributed with the revised labeling.

FDA established the CBE-0 supplement procedures to allow distribution of revised labeling containing important safety-related labeling changes upon receipt of the supplement by the Agency. Over the years, FDA has amended its CBE-0 supplement regulations to clarify the types of labeling changes that may be made by a CBE-0 supplement. NDA and BLA holders are currently permitted to submit CBE-0 supplements for certain types of changes to product labeling to reflect newly acquired information (e.g., to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association).

With the “Physicians Labeling Rule” (PLR) of 2006, FDA began requiring new and recently approved drugs to include Highlights (71 FR 3922). The Highlights is intended to summarize the information that is most important for prescribing the drug safely and effectively, and to organize the information so that it is easily accessible to healthcare providers. Currently,

most changes to the Highlights of drug labeling require a prior approval supplement, unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver requested by the applicant to permit submission of a CBE-0 supplement for a change to the Highlights.

B. Need for Regulation

Generic drugs are generally required to have the same labeling as the reference listed drug, and are not currently permitted to independently change labeling to include new safety-related information that does not conform to the approved labeling of the reference listed drug. The proposed rule would permit ANDA holders to distribute updated product labeling that differs from the labeling of its reference listed drug upon submission of a CBE-0 supplement for safety-related labeling changes. Two recent Supreme Court cases (Wyeth v. Levine and Pliva v. Mensing) held that the difference between the NDA and ANDA holders' abilities to independently change their product labeling leads to different outcomes on whether federal labeling requirements preempt state law tort claims against drug manufacturers for "failure to warn." As a result of these Supreme Court decisions, an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and thus access to the courts is dependent on whether an individual is dispensed a "brand name" or generic drug.

C. Purpose of the Proposed Rule

The primary objective of this proposed rule is to create equal opportunity for NDA holders and ANDA holders to update product labeling to reflect newly acquired information on important drug safety issues through a CBE-0 supplement. Currently, all application holders are required to promptly review all adverse drug experience information they obtain or otherwise receive from any source, and comply with applicable reporting and recordkeeping requirements. NDA holders are allowed to submit a CBE-0 supplement and distribute revised labeling based on newly acquired information that relates to important safety information about the drug. ANDA holders may only submit a CBE-0 supplement to update its generic drug labeling to conform to the approved labeling for the reference listed drug or to fulfill an FDA request.

The proposed rule would maintain the current supplement process for NDA and BLA holders and the requirement that all NDA, ANDA, and BLA holders evaluate and report post-marketing adverse drug experiences. However, ANDA holders would now be permitted to submit a CBE-0 supplement for safety-related labeling changes that differ from the approved labeling of the reference listed drug, if the proposed labeling change meets the criteria of the current CBE-0 regulation. As with an NDA holder or BLA holder, a CBE-0 supplement submitted by an ANDA holder will be converted to a prior approval supplement if the supplement does not meet the CBE-0 supplement criteria. Manufacturers who submit CBE-0 supplements which are found to not meet the CBE-0 supplement criteria must cease distribution of the drug product(s) accompanied by the unapproved, revised labeling, and must take steps to make the drug product(s) available only with the previous version of the labeling. Under the proposed regulation, an ANDA holder submitting a CBE-0 labeling supplement to FDA will also be required to send notice of the labeling change proposed in the CBE-0 supplement to the NDA

holder for the reference listed drug. FDA will approve the labeling change proposed in the ANDA holder's CBE-0 supplement upon approval of the same labeling change for the reference listed drug as explained in section II.B of the proposed rule (78 FR 67985, November 13, 2013).

The proposed rule also would allow all application holders to submit CBE-0 supplements for changes to the Highlights of drug labeling in the PLR format. Currently, most changes to the information required in the Highlights must be made by prior approval supplement, unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request.

The proposed rule also would create an FDA Web page on which pending CBE-0 supplements for safety-related labeling changes for NDAs, ANDAs, and BLAs reviewed by the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER) would be posted. The purpose of the Web page is to make safety-related labeling changes readily available to prescribing healthcare providers and the public while they are under review, and to minimize confusion regarding differences in safety-related labeling for drugs that FDA has determined to be therapeutically equivalent. Once FDA receives the CBE-0 supplement, FDA would post the information about the pending CBE-0 supplement to the Web page until FDA has completed its review and taken an action on the supplement. Other application holders and the public may subscribe to FDA's free e-mail subscription service to receive an e-mail message each time there is an update to this proposed FDA Web page. When FDA approves revised labeling for the NDA that is the reference listed drug, either as the sole submitter of a proposed labeling change or at the time of approval of the same labeling change proposed by an ANDA holder, other ANDA holders will be required to submit a CBE-0 supplement with the revised labeling.

D. Baseline Conditions

The effects of the proposed rule are estimated relative to a baseline. The baseline represents the state of the world in the absence of the proposed regulatory action. In our analysis, we describe baseline conditions in terms of the projected market for drugs approved in BLAs and NDAs, and submissions of CBE-0 supplements for safety-related labeling changes. If there were no changes to the current regulations to allow ANDA holders to submit CBE-0 supplements for safety-related labeling changes prior to approval of an NDA holder's labeling supplement, future submissions of CBE-0 supplements for safety-related labeling changes by BLA holders and NDA holders could reasonably be approximated by current levels. Because FDA routinely grants waiver requests or otherwise specifically requests submission of a CBE-0 supplement for changes to the Highlights of drug labeling in the PLR format, we do not anticipate a significant change in the number of future submissions of CBE-0 supplements by NDA holders and BLA holders. We acknowledge that a proposed labeling change may be submitted multiple times due to FDA-requested revisions. The numbers presented in this section consider only the number of CBE-0 supplements that resulted in approvals.

Table 2: Subsample of CBE-0 Supplements

Description	Total	Average	Min	Max
Total Number of CBE-0 Supplements	56 ^a			
Cases with Marketed NDAs in addition to CBE-0 Submitter	5			
Counting CBE-0 Submitter, Number of Marketed NDA Products	118	2.1	1	10
Number of Submissions with an ANDA	27			
ANDA Products per CBE-0 Submission	228	4.1	0	32
Unique Products per CBE-0 Submission	346	6.2	1	36
Unique Products per CBE-0 Submission from Firms other than the CBE-0 Submitter	242	4.3	0	32
Firms, Including CBE-0 Submitter	168	3.0	1	17

^a 27 products in 2009; 29 products in 2010

1. Current Level of Reviewed CBE-0 Supplements for Safety-Related Labeling Changes Submitted by NDA Holders

If the proposed rule is finalized, it would allow ANDA holders of approved generic drugs to pursue a safety-related labeling change through the submission of a CBE-0 supplement even when there has not yet been a CBE-0 supplement submitted by the NDA holder for the corresponding RLD. Currently, FDA generally has advised that an ANDA holder may not independently submit a CBE-0 supplement for safety-related labeling changes that differ from the approved labeling of the reference listed drug. A recent analysis of reviewed CBE-0 submissions for the years 2009 and 2010 in FDA's Document Archiving, Reporting and Regulatory Tracking System (DARRTS) found approximately 363 (2009 = 174; 2010 = 189) CBE-0 labeling supplement submissions for safety-related labeling changes.¹ Given this result, we approximate a baseline average number of reviewed CBE-0 supplement submissions for safety-related labeling changes equal to 181.5 (= 363 CBE-0 safety-related labeling changes / 2 years) per year.

a. Subsample of CBE-0 Supplements for Safety-Related Labeling Changes for Drugs

We use a subsample of the 363 reviewed CBE-0 supplement submissions for safety-related labeling changes in 2009 and 2010 from DARRTS to provide descriptive statistics. The subsample was selected based on the following requirements: (1) the supplement applicant code was CBE-0; (2) the supplement FDA code was CBE-0; (3) the supplement labeling change had been approved by FDA (with or without revisions to the applicant's proposed labeling change). Table 2 presents the subsample descriptive statistics. Out of a total of 56 supplements for safety-related labeling change submissions, 48 percent (= 27 with ANDAs / 56 Total Submissions) had an ANDA on the market and only 5 total submissions had an NDA other than the submitter on

¹ The original query returned 448 (2009 = 210; 2010 = 238) supplements for safety-related labeling changes that were submitted as CBE-0 supplements. The sample size was reduced to 363 to remove supplements that did not clearly meet the criteria for CBE-0 labeling supplements or for which there was uncertainty about the supplement coding in DAARTS.

Table 3: Subsample of CBE-0 supplements for NDAs with an ANDA

Description	Total	Average	Min	Max
Total Number of CBE-0 supplements for NDAs with an ANDA	27 ^a			
Cases with Marketed NDAs in Addition to CBE-0 Submitter	5			
Counting CBE-0 Submitter, Number of Marketed NDA Products	64	2.4	1	8
ANDA Products per CBE-0 Submission	228	8.4	1	32
Unique Products per CBE-0 Submission	292	10.8	2	36
Unique Products per CBE-0 Submission from Firms other than the CBE-0 Submitter	242	9.0	1	32
Firms, Including CBE-0 Submitter	139	5.1	2	17

^a 14 products in 2009; 13 products in 2010

the market at the time of approval. Counting the firm submitting the CBE supplement, 3 different firms were affected, on average, with each CBE-0 supplement approval. The average number of brand name drug products, including the CBE-0 submitter, is 2.1 per supplement for safety-related labeling changes, which may include different strengths of the drug. The average number of generic drug products that correspond to the brand name drug product for which a safety-related labeling change was submitted is 4.1.² Taken together, each supplement for a safety-related labeling change affects 6.2 drug products, on average.

Table 3 presents descriptive statistics only for those in the subsample where there was also at least one marketed ANDA that relied on approval of the NDA that submitted the CBE-0 supplement for safety-related labeling changes. The subsample contains 27 observations with at least one marketed ANDA at the time of the labeling change approval. Counting the firm submitting the CBE supplement, 5.1 different firms were affected, on average, with each CBE-0 supplement approval. The average number of ANDAs per submission is 8.4 and the average number of NDAs per submission is 2.4. Taken together, each CBE-0 supplement for a safety-related labeling change for a product with a marketed ANDA affected 10.8 products, on average.

b. Current Level of CBER-reviewed CBE-0 Supplements for Safety-Related Labeling Changes Submitted by NDA Holders

In each of the sample years, 2009 and 2010, only one CBE-0 supplement was submitted to CBER by an NDA holder. In 2009, there were 3 ANDAs listed in the Orange Book for the NDA submitting the CBE-0 supplement (Ref. 1). In 2010, there was only 1 ANDA listed for the NDA submitting the CBE-0 supplement. Over the two years, an average of 3 unique products and 2.5 firms were affected by the two CBE-0 supplements per year.

² One outlier observation containing a total of 89 ANDAs was thrown out of the sample. Of the remaining 27 CBE-0 supplement submissions for safety-related labeling changes, 9 had 10 or more ANDAs, 5 had 20 or more ANDAs, and 2 had 32 ANDAs.

2. Current Level of CBE-0 Supplements for Safety-Related Labeling Changes by Submitted by BLA Holders

In addition to all CBE-0 supplements for safety-related labeling changes submitted to NDAs and ANDAs, the proposed rule, if finalized, would also post CBE-0 supplements for safety-related labeling changes for BLAs on the proposed FDA public web page. Over the two year period, 2009-2010, a total of 64 CBE-0 supplements (2009 = 33; 2010 = 31) for BLAs were submitted to CBER for safety-related labeling changes, for an average of 32 per year. Over the same period, a total of 29 CBE-0 supplements (2009 = 12; 2010 = 17) for BLAs were submitted to CDER for safety-related labeling changes, for an average of 14.5 per year.

3. Current Level of PAS for Changes to the Highlights of Drug Labeling

If the proposed rule is finalized, it would allow application holders for drugs with labeling in the PLR format to submit a CBE-0 labeling supplement for changes to the Highlights of drug labeling. Currently, if an application holder desires to make changes to the Highlights of drug labeling, it must submit a prior approval supplement unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request. The Agency estimates that the product review divisions receive only a few submissions per year seeking to change the Highlights of drug labeling. In almost all of these cases, FDA permits these changes to be made through a CBE-0 supplement.

E. Effects of the Proposed Rule

The proposed rule would permit an ANDA holder to submit a CBE-0 supplement for safety-related labeling changes that differ from currently approved labeling of the reference listed drug. In order to estimate the net economic impact of this proposed rule on society, an approximation of the change in behavior of consumers, producers, and FDA is needed.

FDA estimates there are approximately 420 ANDAs with unique active ingredients that are identified as the reference standard in the Orange Book (for use in an in vivo bioequivalence study required for generic drug approval) as a result of the reference listed drug having been discontinued from marketing (Ref. 1). For a subset of these products, approval of the NDA for the reference listed drug has been withdrawn (for reasons other than safety or effectiveness). There will undoubtedly be cases where these ANDA holders will submit a CBE-0 supplement for a safety-related labeling change, thus increasing the total number of CBE-0 supplements received by FDA. Currently, these ANDA holders must contact FDA if they believe that new safety information should be added to their product labeling unless a labeling change already has been requested by FDA. We acknowledge that there may be CBE-0 supplements submitted by ANDA holders for safety-related labeling changes in addition to those estimated in this analysis. However, we do not include these efforts to change the labeling in the following analysis. We invite comment on the estimated number of CBE-0 supplements that may be submitted by ANDA holders.

Based on current submissions for safety-related labeling changes, FDA anticipates that this proposed rule would potentially facilitate more timely communication of important drug

safety information to healthcare providers and patients, and may be used to inform treatment decisions based on the balance of potential benefits and risks of the drug product for each patient. The actual changes, however, are uncertain.

What follows is an explanation of how the Agency attempts to account for this uncertainty in estimating the effects of the proposed rule. The theoretical exercise presented below is used to frame the empirical discussion. The discussions over the next two subsections are included to describe the range of changes to the number of additional CBE-0 supplements submitted in markets with both NDA and ANDA holders that may result, if the proposed rule is finalized.

1. Number of CBE-0 supplements Submitted by ANDA Holders

Under current policy, after approval of a safety-related labeling change by the NDA holder for the reference listed drug, ANDA holders must submit a CBE-0 supplement to make the same changes to their labeling, although all application holders are required to propose necessary safety-related revisions to their labeling. With the adoption of the proposed rule, ANDA holders would be permitted to be the first to submit a CBE-0 supplement for safety-related labeling changes. However, in cases where approval of the NDA for the reference listed drug has not been withdrawn, NDA holders may have an economic incentive to move first.

Consider a market for a single pharmaceutical product with only two actors, the NDA holder and an ANDA holder. Due to the uncertainty surrounding the effect of this proposed rule, we assume the following for purposes of this analysis: (1) the products must have the same labeling on the market; (2) each actor becomes aware of an adverse experience at about the same time from a party not affiliated with either actor; (3) the economic risk for not responding to the adverse experience is the same for each producer; (4) the economic reward for responding to the adverse experience is the same for each producer; (5) the submitted labeling change will be approved by FDA. Under most circumstances under the current regulation, only the NDA holder may submit a CBE-0 supplement for a safety-related labeling change that differs from currently approved labeling. Unless the ANDA holder contacts FDA regarding its labeling concern and FDA specifically asks for a labeling change, the ANDA holder generally must wait for the Agency to approve the NDA holder's labeling change before the ANDA holder can change the generic drug labeling.

Now consider what might happen if both actors become aware of an adverse event relating to the use of their product at the same time but they are under the proposed regulation that permits an ANDA holder to submit a CBE-0 supplement for safety-related labeling changes that differs from the NDA holder's labeling. Now either actor can submit a CBE-0 supplement to update its approved labeling to reflect the newly acquired information.

If the NDA holder moves first, its only expected cost is the submission of the CBE-0 supplement to FDA for approval. The ANDA holder, as the second mover, would be expected to monitor the FDA Web page, review the NDA holder's CBE-0 supplement, and submit, if appropriate, a CBE-0 supplement to FDA to update its labeling to address the safety-related issue before and/or after FDA takes an action on the NDA holder's CBE-0 supplement. However, if

Figure 1: Sequential Game Example

	ANDA will:	NDA will:
If NDA Moves First	(1) Review NDA holder's proposed labeling change on FDA Web site or final approved labeling change (2) Submit CBE-0 to FDA before and/or after approval of the NDA holder's proposed labeling change.	(1) Submit CBE-0 to FDA
If ANDA Moves First	(1) Submit CBE-0 to FDA and send notice to NDA holder (2) Wait for approval of revised labeling for the reference listed drug before CBE-0 approval	(1) Review notice from the ANDA holder (2) Submit CBE-0 to FDA

the ANDA holder moves first, it must submit a CBE-0 labeling supplement to the Agency and notice of the CBE-0 supplement to the NDA holder. If the NDA holder submits the CBE-0 supplement for a safety-related labeling change after the ANDA holder, it must review the CBE-0 supplement submitted by the ANDA holder as part of its review and evaluation of post-marketing data, and would generally submit a supplement for the labeling change to FDA before the Agency will approve the labeling change for either actor.

Figure 1 illustrates the potential outcomes described in the preceding paragraph. Only the NDA holder receives a clear economic advantage, from perceived protection of the brand name, by moving first. This scenario is most likely to occur in cases where the NDA holder perceives its reputation as sufficiently important for it to be in its interest to maintain a reputation for dealing promptly and effectively with safety-related information. Therefore, in our base case we expect the NDA holder to desire to be the firm on record for leading a safety-related labeling change.

There may, however, be situations where the ANDA holder will be the first mover. For instance, in cases where approval of the NDA for the reference listed drug has been withdrawn (for reasons other than safety or effectiveness), the ANDA holder will be the first to move. Or if the ANDA holder receives the safety-related information (e.g., spontaneous adverse event reports) first, they may be more likely to move first. The ANDA holder may also have an economic incentive to be the first actor to move if, due to a larger market share, the expected economic benefit of moving first is larger than the expected cost of moving first, or if the

expected economic risk of not moving first is larger than the expected cost savings of not moving first. The purpose of this exercise is to illustrate that since the costs of moving first may be avoidable, we are uncertain about the ultimate number of new CBE-0 supplements for safety-related labeling changes.

We are proposing to allow any ANDA holder to make certain safety-related labeling changes by submitting a CBE-0 supplement before the NDA holder has changed the labeling for the reference listed drug, so we must also consider the possibility that multiple ANDA holders may submit different CBE-0 supplements for the same safety concern (e.g., based on published literature) at approximately the same time. Multiple CBE-0 submissions for the same safety-related labeling change would increase the cost of reviewing and responding to the CBE-0 supplement or notice of the CBE-0 supplement by FDA and the NDA holder, respectively. We would expect the likelihood of having multiple ANDA CBE-0 supplement submissions to increase with the number of firms marketing the product. In our sample of 27 CBE-0 supplements for safety-related labeling changes with a marketed ANDA, approximately half were for a product with 4 or more firms in the market.

2. Estimation Ranges

The previous discussion provides support for the ranges we use to estimate the numbers of new CBE-0 supplements that may be submitted by ANDA holders as a result of this proposed rule. Other variables influence a firm's decision to submit a CBE-0 supplement for safety-related labeling changes first or not. These variables may include seriousness of the adverse drug experience, the magnitude of the risk, the potential to prevent or mitigate the risk, number of products on the market, size of the firm, market share, likelihood of legal action against the firm for not updating product labeling, and estimation of the financial hit to the firm. In addition, NDA holders may have more resources to devote to review and evaluation of post-marketing data for adverse experiences with their products. However, the simple model presented in Figure 1 serves to illustrate why the NDA holder may have a greater incentive to remain the first firm to submit a CBE-0 supplement for safety-related labeling changes, but we also describe scenarios where the ANDA holder may move first.

The number of safety-related labeling changes ANDA holders will lead through CBE-0 supplement submissions, the possible increase in the total number of submissions due to multiple ANDA holders submitting CBE-0 supplements, and additional submissions by NDA holders are all uncertain. FDA is therefore unable to provide a precise estimate of the change in submission and review costs to industry and the Agency. While we agree there will be new CBE-0 supplements for safety-related labeling changes submitted by ANDA holders for generic drugs for which the approval of the NDA has been withdrawn, we have no reason to expect a specific number of ANDA-led safety-related labeling changes for drugs if the reference listed drug approved in an NDA is currently marketed. Instead, we expect that, where there is an NDA holder, ANDA holder-initiated safety-related labeling changes will occur primarily under the conditions described above.

To account for the likelihood that an ANDA holder will initiate a safety-related labeling change and to include an upper-bound for the possibility of multiple ANDA submissions for the

same product, we look at the two types of safety-related labeling changes most likely to influence ANDA holders to be a first-mover: boxed warnings and contraindications. Over the 2009-2010 time period, there were approximately 114 approved labeling changes for boxed warnings (48) and for contraindications (66). It should be noted that several of these labeling changes were made at the request of FDA. This averages out to 57 approved labeling changes for boxed warnings and contraindications per year. A total of 39 approved labeling changes occurred for drugs with ANDAs. We use the average over the two years, 19.5 CBE-0 supplements per year, as our upper bound in the estimations below. Because of the uncertainty associated with the impact on the number of CBE-0 supplement submissions from ANDA holders of drugs for which the reference listed drug approved in an NDA is currently marketed, we use a lower bound of 1 CBE-0 supplement per year.

We assume that the proposed rule will have no effect on the number of CBE-0 supplements submitted by BLA holders because BLA holders may submit CBE-0 supplements under the current regulations.

F. Benefits of the Proposed Rule

Adopting the proposed rule would permit ANDA holders for prescription and non-monograph OTC drugs to submit CBE-0 supplements for safety-related labeling changes to FDA independent of changes submitted by an NDA holder for the same product. The primary benefit of this proposed regulation would be the value of communicating important drug safety information to prescribing healthcare providers and the public more quickly by allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement. The information in updated product labeling may be used to inform treatment decisions based on the balance of potential benefits and risks of the drug product for each patient, and may prevent or mitigate certain risks. It is difficult to quantify the value of a health risk reduction because we do not have economic data on the potential adverse health effects due to ANDA holders not being permitted to lead a safety-related labeling change through the submission of a CBE-0 supplement. Due to the uncertainty in the amount of risk reduction, FDA requests comments on this part of the analysis.

The proposed rule may lead ANDA holders to participate more actively with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling. This could increase the likelihood that an adverse experience from a drug product is communicated sooner, thus allowing the prescribing healthcare provider to consider the safety information in making treatment decisions based on the balance of potential benefits and risks of the drug product for each patient, which may result in prevention or mitigation of certain risks in some cases. Due to the smaller revenues generic drug firms receive from the same products as brand name drug firms and the relatively small number of adverse events reported to generic drug firms, it is unlikely these companies are devoting the same amount of resources to their own adverse event research as the brand-name firms. However, generic companies currently may review available research and publications on their products and report their findings and concerns to FDA. Therefore, the possibility that FDA is made aware of potential adverse experiences associated with drugs more quickly with the adoption of the proposed rule is uncertain.

It is also possible that the proposed regulation may improve the time between discovery of an adverse experience related to use of the drug and the actual labeling change due to an increase in the number of firms able to submit labeling changes via CBE-0 supplement. ANDA holders currently are advised to submit a CBE-0 supplement to revise product labeling to conform to an approved revision to the reference listed drug's labeling "at the very earliest time possible" (Ref. 2). The proposed rule would require ANDA holders to submit their revised labeling within 30 days of FDA's posting of the approval letter for the reference listed drug's labeling change on its Web site. An examination of new boxed warnings approved during the 2009-2010 time period found that the time between approval of the NDA holder's labeling change and submission of the ANDA holder's labeling supplement for conforming changes varies, and the majority of ANDA supplement submissions occur after 30 days.

In addition, ANDA holders for generic drugs for which approval of the NDA for the reference listed drug has been withdrawn will now be allowed to make safety-related labeling changes through CBE-0 supplements. Permitting ANDA holders for generic drugs for which the reference listed drug has been withdrawn to submit a CBE-0 supplement may benefit consumers and healthcare providers because it would allow ANDA holders to change their labeling sooner. Any reduction in time between the ascertainment of a safety-related issue with a drug and a change to the drug's labeling to reflect new safety information may allow consideration of the risk when making treatment decisions and, in certain cases, has the potential to reduce the frequency or severity of a given adverse event.

G. Costs of the Proposed Rule

The proposed rule may result in an increase to the cost of participating in the market for approved drugs. This potential burden stems from additional supplement submissions and reviews. We expect application holders may react in a number of ways, each associated with different costs. Estimated costs depend on the number of CBE-0 supplements for safety-related labeling changes submitted by ANDA holders to update their products' labeling when the reference listed drug also is currently marketed. Additional CBE-0 submissions from ANDA holders where approval of the NDA for the reference listed drug has been withdrawn may represent an additional cost of the proposed rule.

For the following cost estimations, we assume application holders are already complying with the requirement to review and evaluate post-marketing adverse drug experiences, and report their findings to the Agency. We use the 2-year average from the most currently available data of 182.5 (= 1 CBER CBE-0 supplement per year + 181.5 CDER CBE-0 supplements per year) submissions between CBER and CDER previously reported as a proxy for any future safety information that may require a safety-related labeling change. We also assume the proposed rule will have no effect on the number of CBE-0 supplements for BLAs that are submitted. Finally, even though the proposed rule would require the CBE-0 supplement submitter to contact FDA within 5 business days of the supplement being posted on the proposed FDA Web page if the posted information is incorrect, we do not consider the additional cost of getting the incorrect information corrected. Instead, we assume all submitted information will be accurately posted to the proposed FDA Web page.

1. Costs to ANDA Holders

ANDA holders will incur additional burdens for each safety-related CBE-0 supplement submitted to update their labeling from the approved labeling. The bulk of the ANDA holders' additional costs will come from preparing and submitting new labeling change supplements. ANDA holders will also face costs due to the requirement to check the FDA Web page and see if their supplement was posted accurately.

a. Supplement Submission Costs (to FDA and NDA holders)

Currently, ANDA holders for generic drugs for which approval of the NDA for the reference listed drug has not been withdrawn are required to prepare and submit a CBE-0 supplement for a safety-related labeling change when a labeling change for the reference listed drug has been approved. ANDA holders also should contact FDA if they believe that new safety information should be added to product labeling and FDA will evaluate whether the labeling for the reference listed drug and the generic drug should be revised. If approval of the NDA for the reference listed drug has been withdrawn, FDA will work with ANDA holders to update product labeling. Even though the proposed rule, if finalized, may lead to an increase in the total number of CBE-0 supplements for safety-related labeling changes received by FDA, we assume there would be no additional submission costs associated with ANDA holders submitting a CBE-0 supplement rather than pursuing other methods. Since we do not anticipate additional costs for submissions of CBE-0 supplements from ANDA holders as a result of the proposed rule being finalized, we do not include the cost to the ANDA holder of submitting a CBE-0 supplement to FDA.

However, under the proposed rule the ANDA holder will be required to provide notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for review so we do need to consider the additional cost of preparing this notice. Depending on the type of information supporting the ANDA holder's proposed labeling change, the ANDA holder may be required to redact personally identifiable information (e.g., from an adverse drug experience report) from the information provided in the notice it sends to the NDA holder.

Preparation of the supplement would require clerical, medical, and legal input and review. Therefore, in valuing the time cost, FDA uses the weighted average of Pharmaceutical and Medicine Manufacturing (NAICS, Code 325400) industry-specific mean hourly wages for Office and Administrative Support Occupations (\$21.08), Legal Occupations (\$68.58), and Management Occupations (\$62.38) (Ref. 3). FDA assigns these occupational categories weights of 25 percent, 25 percent, and 50 percent. The resulting composite wage in 2011 is \$53.61 (= [\$21.08 per hour * 0.25] + [\$68.58 per hour * 0.25] + [\$62.38 per hour * 0.5]). FDA then doubles this amount to \$107.21 (= \$53.61 per hour * 2) to account for benefits and capital costs.

The Agency anticipates it could take between 4 and 12 hours for an applicant to prepare and submit an original supplement to FDA. Because the ANDA holder may be required to redact some information from the supplement before it sends it to the NDA holder, we estimate that preparation of the NDA holder's copy could generate an incremental cost equal to one-

quarter of the cost of preparing the FDA submission. Given the fully-loaded hourly wage rate for preparation and the amount of time it may take the generic drug manufacturer to prepare a supplement for the NDA, we estimate cost per submission to the NDA to be between \$107 (= 1 hour * \$107.21 per hour) and \$322 (= 3 hours * \$107.21 per hour). Over the course of a year, we estimate the additional supplement submission cost to the ANDA as a result of the proposed rule may range from \$107 (= \$107 per submission * 1 submission) to \$6,272 (= \$322 per submission * 19.5 submissions) per year.

b. Submission Review Costs: ANDA

We estimate that it would take an applicant 30 minutes or less to check the FDA Web page to see if the information about their CBE-0 supplement was posted correctly. Given the estimated range of 1 to 19.5 ANDA CBE-0 submissions each year, we estimate ANDA holders will spend between 0.5 (= [30 minutes * 1 ANDA supplement submission] / 60 minutes) hours and 9.75 (= [30 minutes * 19.5 ANDA supplement submissions] / 60 minutes) hours checking the Web page for accuracy regarding safety-related CBE-0 supplement submissions per year. FDA anticipates the task of reviewing the FDA Web page for accuracy will fall on clerical staff. Using the fully-loaded hourly wage for Office and Administrative Support Occupations of \$42.16 (= \$21.08 per hour * 2), we estimate the additional submission review costs to the ANDA as a result of the proposed rule may range from \$21 (= 0.5 hours per year * \$42.16 per hour) per year to \$411 (= 9.75 hours per year * \$42.16 per hour) per year.

2. Costs to NDA Holders of the Reference Listed Drug

NDA holders would be required to check the FDA Web page to see if information about their CBE-0 supplement was posted accurately. In addition, NDA holders are required to review any adverse drug experience information received from the ANDA holder in its notice of the labeling change proposed in the ANDA holder's CBE-0 supplement. Because we assume there will be no CBE-0 supplements in addition to the current level submitted by NDA holders each year as a result of the proposed rule, we do not include an estimate of the cost of an NDA holder preparing and submitting a CBE-0 labeling supplement.

a. Submission Review Costs: NDA

We estimate that it would take an applicant 30 minutes or less to check the FDA Web page to see if the information in their CBE-0 supplement was posted correctly. Given the estimated average of 182.5 CBE-0 submissions each year, we estimate NDA holders will spend approximately 91.25 (= [30 minutes * 182.5 total supplement submissions] / 60 minutes) hours checking the FDA Web page for accuracy regarding safety-related CBE-0 supplement submissions per year. FDA anticipates the task of reviewing the FDA Web page for accuracy will fall on clerical staff. Using the fully-loaded hourly wage for Office and Administrative Support Occupations of \$42.16 (= \$21.08 per hour * 2), we estimate the additional submission review costs to the NDA holder as a result of the proposed rule may be \$3,847 (= 91.25 hours per year * \$42.16 per hour) per year.

b. Supplement Review Costs

With approval of the proposed rule, ANDA holders would be required to send notice of the labeling change proposed in the CBE-0 supplement to the NDA holder for the reference listed drug, unless approval of the NDA has been withdrawn. The NDA holder is expected to consider the information provided by the ANDA holder as part of their review and evaluation of adverse drug experience information. In many circumstances, the NDA holder may already have knowledge of the safety-related information described by the ANDA holder in the CBE-0 labeling supplement. However, it is possible that the NDA holder may not be aware of the ANDA holder's newly acquired information (e.g., a spontaneous adverse event report submitted to the ANDA holder) prior to receipt of the ANDA holder's notice. This may add to the NDA's review time for the notice.

FDA anticipates it will take half of the time for the NDA holder to review a notice of a labeling change proposed in a CBE-0 supplement submitted by an ANDA holder as it took the ANDA holder to prepare the CBE-0 supplement. Therefore, we use a range of 2 to 6 hours for review time. We distribute the time evenly among Legal Occupations (\$68.58), and Management Occupations (\$62.38) to get an hourly wage of \$65.48 ($= \$68.58 \text{ per hour} * 0.5 + \$62.38 \text{ per hour} * 0.5$). FDA then doubles this amount to \$130.96 ($= \$65.48 \text{ per hour} * 2$) to account for benefits and capital costs. Multiplying the amount of time needed to review the notice by the time cost gives a per supplement review cost range of \$262 ($= \$130.96 \text{ per hour} * 2 \text{ hours}$) to \$786 ($= \$130.96 \text{ per hour} * 6 \text{ hours}$). Taken over the course of a year, we estimate the additional information review cost to the NDA holder as a result of the proposed rule may range from \$262 ($= \$262 \text{ per submission} * 1 \text{ submission}$) to \$15,322 ($= \$786 \text{ per submission} * 19.5 \text{ submissions}$) per year.

3. Costs to FDA

The proposed rule would establish a dedicated FDA Web page (or, alternatively, would modify an existing FDA Web page) that will provide information on the CBE-0 supplements for safety-related labeling changes for ANDAs, NDAs, or BLAs that are pending FDA action. The CBE-0 supplement would remain posted on the FDA Web page until FDA has completed its review and issued an action letter. Approved labeling would be available at <http://labels.fda.gov>. The public may subscribe to FDA's free e-mail subscription service to receive an e-mail message each time there is an update to this proposed FDA Web page.

Creating and maintaining the Web page would be routine for FDA staff and would use already established resources. Therefore, the additional burden of this FDA Web page would add only negligible costs using current resources and are thus not included in this analysis. However, if additional resources are needed to create and maintain the FDA Web page, FDA estimates it would cost approximately \$5,000 to \$10,000 to create the page and an additional \$6,500 to \$13,000 per year to maintain the page.

Table 4: Summary of Total Costs

	Annual Costs	
	Low Estimate	High Estimate
Costs to ANDA Holders		
Annual Supplement Submission Costs	\$107	\$6,272
Annual Submission Review Costs	\$21	\$411
Costs to NDA Holders		
Annual Submission Review Costs		\$3,847
Annual Supplement Review Costs	\$262	\$15,322
Total Social Costs	\$4,237	\$25,852

4. Potential Costs

There are additional potential costs that may occur as a result of the proposed rule, but are, at the moment, not quantified due to the large amount of uncertainty about how the proposed rule will alter consumer and industry behavior. These costs may arise as a consequence of multiple CBE-0 supplement submissions for the same adverse event. If more than one ANDA holder submits a CBE-0 supplement based on the same newly acquired information, or if an NDA holder counters an ANDA supplement with a CBE-0 supplement of its own, costs related to both preparing and submitting a supplement, as well as FDA's cost to review the additional supplements, will increase. Also, there may be additional costs to application holders if the applicant starts printing the new labeling and another application holder submits a slightly different labeling change, or the proposed labeling change is not approved by FDA.

5. Summary of Total Costs

Table 4 presents a summary of the estimated total costs that may result with the implementation of the proposed rule. FDA estimates that implementing the proposed rule may result in average annual costs ranging from \$4,237 to \$25,852. These costs represent a best estimate given the information available. Additional uncertainties are associated with these cost estimates, but are not reflected in the ranges reported in Table 4. As shown in the table, however, even the upper bounds of the uncertain ranges of submission and review costs are quite small.

H. International Effects

The pharmaceutical industry is global, with manufacturing and consumption of a product often taking place in different parts of the world. The proposed rule would permit ANDA holders to submit a CBE-0 labeling supplement for safety-related labeling changes to the FDA. Foreign applicants marketing products covered by the proposed rule in the United States would incur the same costs associated with labeling supplement submissions and labeling changes as incurred by firms operating in the United States. The proposed rule would be unlikely to alter the current mix of foreign and domestic manufacturing for the affected products.

I. Distributional Effects

We do not anticipate that the proposed rule would result in significantly higher compliance costs to generic firms in terms of insurance premiums that would lead to market exit or reduced market entry and higher generic drug prices. First, generic drug companies purchase insurance to cover a wide range of liabilities, and the cost of covering failure to warn claims will be, as it was in the past, part of an overall insurance cost. Accordingly, we do not anticipate that the proposed rule would result in higher costs to generic drug manufacturers. Second, existing regulations currently require that all NDA and ANDA holders evaluate and report post-marketing adverse drug experiences.

III. Initial Regulatory Flexibility Analysis

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. This analysis, together with other relevant sections of this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

This proposed rule would only impose new burdens on small generic drug manufacturers who submit CBE-0 supplements for safety-related labeling changes. Given the small cost per submission and the uncertainty in the estimated number of CBE-0 labeling supplements for safety-related labeling changes that may be submitted by an ANDA holder, we do not expect this proposed rule to impose a significant impact on a substantial number of small entities. We therefore propose to certify that that this proposed rule would not have a significant economic impact on a substantial number of small entities.

IV. References

1. U.S. Food and Drug Administration, “Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 33rd Edition,” available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>.
2. U.S. Food and Drug Administration, “Guidance for Industry: Revising ANDA Labeling Following Revision of the RLD Labeling,” issued May 2000, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072891.pdf>.
3. U.S. Bureau of Labor Statistics, “Occupational Employment Statistics: May 2011 National Industry-Specific Occupational Employment and Wage Estimates NAICS 325400—Pharmaceutical and Medicine Manufacturing,” available at http://www.bls.gov/oes/current/naics4_325400.htm.