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PUBLIC INTEREST COMMENT

Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

Docket No. FDA–2013–N–0500

Todd M. Nesbit

Food and Drug Administration, Health and Human Services
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INTRODUCTION

The Regulatory Studies Program of the Mercatus Center at George Mason University is dedicated to advancing knowledge about the effects of regulation on society. As part of its mission, the program conducts careful and independent analyses that employ contemporary economic scholarship to assess rulemaking proposals and their effects on the economic opportunities and social well-being available to all members of American society.

This comment addresses the efficiency and efficacy of this proposed rule from an economic point of view. Specifically, it examines how the proposed rule may be improved by more closely examining the societal goals the rule intends to achieve and whether this proposed regulation will successfully achieve those goals. In many instances, regulations can be substantially improved by choosing more effective regulatory options or more carefully assessing the actual societal problem.

SUMMARY

The proposed "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products" rule[1] would enable Abbreviated New Drug Application (ANDA) holders of approved generic drugs to enact a safety-related labeling change by submitting a Changes Being Effected (CBE-0) supplement even when the New Drug Application (NDA) holder of the reference-listed drug has not submitted a CBE-0 for the said change. Current regulations require generic drugs to have identical safety-related labeling as the reference-listed drug. As such, an ANDA holder of an approved generic drug currently may request to change product safety-related labeling only after the respective NDA holder of the reference

1. Department of Health and Human Services, Food and Drug Administration, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 21 C.F.R. 314 and 601, Docket No. FDA-2013-N-0500, RIN 0910-AG94. Hereafter cited as NPRM.

For more information, contact:
Robin Bowen, (703) 993-8582, rbowen@mercatus.gmu.edu
Mercatus Center at George Mason University
3434 Washington Boulevard, 4th Floor, Arlington, VA 22201

drug has had such changes approved by the Food and Drug Administration (FDA).[2] This rule would allow ANDA holders to independently submit a CBE-0 supplement.

The FDA argues that this rule will allow ANDA holders to more actively participate in the updating of safety-related labeling, potentially increasing the speed of communication of important drug safety information, specifically for generic drugs, to physicians and the public. Given that 80 percent of all prescription medications dispensed are generic—and that 94 percent are generic when generic drugs are available—adequate dissemination of drug-safety information for generic drugs is certainly an important matter.[3]

While increasing the parity between NDAs and ANDAs in relation to safety-related drug labeling may, in fact, prove to exhibit a positive net benefit on society, the analysis presented in the Preliminary Regulatory Impact Analysis (PRIA) fails to substantiate such a claim. First, the FDA fails to quantify any of the public health benefits of the proposed rule, providing a brief qualitative discussion instead. Second, the estimated costs associated with the proposed rule are greatly understated. Several factors influence this downward-biased estimate, including ignoring FDA administrative costs in the final estimate, assuming away the costs associated with simultaneous CBE-0 submissions from multiple ANDAs, and calculating the high and low estimates based on questionable assumptions. The cost estimations also fail to adequately account for changes in ANDA incentives. Specifically, the analysis does not account for how ANDA holders may increase resources devoted to post-marketing surveillance evaluation and reporting and to legal concerns in response to increased exposure to products liability suits.

The proposed rule may, if finalized, improve the parity between NDAs and ANDAs and possibly better align the interests of ANDAs with physicians and the ultimate consumers of generic drugs. These are certainly laudable goals. Under the current rules, ANDAs cannot independently submit a CBE-0 for a safety-related label change, and an individual's ability to access state courts to file "failure to warn" tort claims depends on whether the individual is dispensed a "brand name" or generic drug.[4] With an FDA-reported 80 percent of prescription drugs dispensed being generic, a sizable share of prescription drug consumers are unable to appeal to the courts for "failure to warn" lawsuits. As such, it is quite possible that the benefits of the proposed rule are sizable. Unfortunately, the FDA presents a careless approach to the estimation of costs and benefits of this proposed rule related to safety-related drug labeling changes.

Given the potential impact on consumer health, this regulation deserves a more thoughtful analysis than the FDA has provided to date. The FDA should improve the Regulatory Impact Analysis to estimate the benefits of the proposed rule and to more accurately estimate all of the costs stemming from it. Further, it is advisable that the FDA compare and contrast the net benefit of the proposed rule with that of other reasonable alternatives. Only after addressing these concerns is it possible to make an educated decision regarding the appropriateness of the proposed rule.

FAILURE TO ASSESS THE BENEFITS

The agency intuitively explains in the PRIA that this regulation is expected to generate benefits in two primary areas: (1) parity between NDAs and ANDAs, and (2) increasing the speed in which new safety-related content is added to generic drug labels. While the qualitative relationship between the proposed

2. Department of Health and Human Services, Food and Drug Administration, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products: Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis," Docket No. FDA-2013-N-0500. Hereafter cited as PRIA.
3. NPRM, 67988.
4. PRIA, 5.

regulation and the potential benefits is well argued in the PRIA, it is not enough to justify the enactment of the rule. One must also quantitatively measure benefits to society such that net benefits of the proposed rule can be considered.

The benefits of the proposed regulation are explained as stemming from what can ultimately be described as loosening inadequate restrictions imposed on ANDAs by existing regulations. Currently, ANDAs have limited ability to influence the content of safety-related drug labels in a timely manner beyond submitting new safety information or proposed safety-label changes to the FDA and waiting for an FDA request to change labels. In most cases, the ANDA role is limited to submitting a CBE-0 to conform to changes in the label of the reference-listing drug. Given the inability of ANDAs to control the content of the product label, recent Supreme Court decisions have determined that consumers may not bring "failure to warn" lawsuits against ANDA holders.

While the FDA mentions that a consumer's "access to the courts is dependent on whether an individual is dispensed a 'brand name' or generic drug" as a need for regulation, it fails to adequately qualify—let alone quantify—the benefits of this increased parity.[5] Immunity from liability in "failure to warn" lawsuits may lead to a less-than-optimal incentive for ANDAs to ensure the most up-to-date and relevant content on their product safety labels. As such, ANDAs may experience a regulatory-driven cost advantage over the respective NDAs. With reduced threat of lawsuit for safety-related labeling inadequacies, ANDAs may face less incentive to maintain sufficient (in number and experience) post-marketing surveillance evaluation and reporting staff and may face lower legal expenses. Such distortions in the market structure may have led to an underinvestment in NDA holders and an overinvestment in ANDA holders. Correcting this regulatory-driven distortion such that both the costs and the legal responsibility for maintaining adequate safety labeling are assigned to all drug producers—both reference-listing drug and generic drug producers—will ultimately improve market efficiency and improve overall social welfare. This potential gain is not even discussed, let alone quantified, in the FDA's PRIA.

The added legal responsibility for maintaining adequate safety labeling for generic drugs is argued to incentivize ANDAs to more actively engage in post-marketing surveillance evaluation and reporting, reducing the time in which some safety-related concerns are addressed in labeling. While this idea is intuitively described in the PRIA, the benefits are not quantified. An estimate, albeit imprecise, of the number of drug-related risks patients could avoid due to the more timely communication of drug safety information could be ascertained by the usage of the number of suits filed against NDAs and scaled by relative market share of generic drugs (94 percent generic to six percent brand name). This would likely serve as a low estimate, as many drug-related risks that could have been avoided through improved labeling may not be reported. Despite the imprecision of this estimate, it would still prove a useful starting point for policymakers and the public to evaluate the benefits and costs per health risk averted.

FAILURE TO PROPERLY ACCOUNT FOR ALL COSTS

The cost estimates presented in the PRIA are generally biased downward due to questionable assumptions and omissions. The analysis appears to contradict itself at times, in that behavioral changes are accounted for in the discussion of benefits but the costs associated with those changes are ignored or assumed to be zero in the presentation of costs. Further, many costs remain unquantified as a result of varying degrees of uncertainty. The estimated annual total social costs of between $4,237 and $25,852

5. PRIA, 5.

are, given the concerns detailed below, unreliable and not sufficient for use in forming a recommendation on whether or not to adopt this proposed regulation.

Assuming Away Changes in ANDA Behavior

Given the new incentives ANDA holders face if this rule is finalized, there should be no surprise that ANDA behavior will change. Some such changes of behavior are identified in the PRIA when it adds to the benefits discussion, but then goes on to discount the behavior change when it discusses costs. For instance, the PRIA appears to acknowledge that ANDAs would be more incentivized to "participate more actively with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling," leading to an increased "likelihood that an adverse experience from a drug product is communicated sooner."[6] This increased engagement in the process of maintaining up-to-date safety-related product labels will require additional resources. Indeed, "it is unlikely these companies are devoting the same amount of resources to their own adverse event research as the brand-name firms."[7]

While the FDA is correct to acknowledge the increased incentive of ANDAs to actively participate in the CBE-0 submission process and the possibility of increased resources employed in such a process, the FDA fails to properly account for the associated costs by assuming that "there would be no additional submission costs associated with ANDA holders submitting a CBE-0 supplement rather than pursuing other methods."[8] Stated alternatively, the FDA assumes that researching, developing, and writing new safety-related label changes require no additional resources than are used to submit a CBE-0 based on a previously approved NDA CBE-0 supplement to remain compliant with federal law. This is unlikely, as being the first to propose product label changes requires more resources to develop and defend the change than those who follow and adopt the new, approved labeling.

A second area of behavior change not addressed in the PRIA concerns a potential lack of experience in the ANDA holders' post-marketing surveillance, evaluation, and reporting staff. This lack of experience can lead to either over- or under-reporting during the learning process. As such, either FDA review costs will be higher or the ANDAs will be exposed to higher risk of "failure to warn" lawsuits than is described in the PRIA. The FDA acknowledges in the PRIA the possibility of multiple ANDAs submitting CBE-0 supplements for the same safety-related label change simultaneously and the resulting increased FDA reviewing costs; however, this increased review cost is largely dismissed as roughly half of the products with ANDAs include four or more firms in the market.[9] The assumption appears to be that existing CBE-0 submissions by ANDAs will remain roughly constant such that it will be a rare event to have multiple submissions. If ANDAs do seek to avoid the exposure to "failure to warn" lawsuits, it is quite feasible for the number of CBE-0 submissions and the probability of multiple submissions for FDA review to grow, increasing FDA administrative costs by a significant sum.

Lastly, ANDA costs may rise in response to the increased exposure to "failure to warn" lawsuits. This could be revealed through increased expenditures on attorneys or increased insurance rates on policies designed to protect the company from large expenses, should the company be found liable.

Questionable Assumptions and Omissions

Lower and upper cost estimates. The average number of labeling changes occurring for drugs with ANDAs during 2009 and 2010 is found to be 19.5. This number—an average—is then used as the upper bound for

6. PRIA, 13.
7. Ibid.
8. PRIA, 15.
9. PRIA, 12.

the FDA's estimates. A lower bound of one CBE-0 per year is also employed. Both of these assumptions are curious. A more standard method for establishing upper and lower bounds is to take the average and extend two or three standard deviations in both directions. This approach would also call for more than just two years of data to be employed in the analysis. Admittedly, not all of the CBE-0 supplements submitted by ANDA holders would be submitted independently of an NDA holder. However, before taking this into account, the upper and lower bounds should be computed in the standard fashion. If using the mean +/- three standard deviations generated lower and upper bounds of, say, four and 32 CBE-0 supplements, the agency could then vary the percent of total CBE-0 supplements that are anticipated to be submitted independently of an NDA. If 50 percent are independently submitted, the lower and upper bounds would be two and 16; at 75 percent, three and 24; and so on.

While the analysis presented in the PRIA attempts to provide useful upper and lower bounds on the cost estimates, they only account for uncertainty in regards to the number of original ANDA-submitted CBE-0 supplements. The number of CBE-0 supplements submitted by NDAs is assumed to be certain at 182.5 per year and does not take into account the variability around this mean. Again, it is advisable to establish upper and lower bounds on this estimate based on the mean +/- an acceptable number of standard deviations, particularly given the FDA-admitted uncertainty of the estimates.

Not accounting for costs associated with simultaneous CBE-0 submissions. Included in the PRIA is a small section on potential costs. The agency admits here that costs may be higher than estimated in part due to "multiple CBE-0 supplement submissions for the same adverse event."[10] It explains that costs to both the NDA and the FDA will rise if more than one ANDA holder submits a CBE-0 supplement based on the same newly acquired information, but that this cost is "not quantified due to the large amount of uncertainty about how the proposed rule will alter consumer and industry behavior."[11] That costs are uncertain is not an excuse for not including estimates of it in the analysis and biasing the estimated costs downward in the process. An estimate of these costs, potentially with a sizable range of values, is necessary to provide Congress and the public with the necessary information to evaluate this proposed rule.

Other assumptions and omissions. The analysis uses data from the two most recent years for which data is available to estimate the number of CBE-0 supplements that can be anticipated under the proposed regulation. While the use of the most recent data is surely warranted, only accounting for the two most recent years hides any possible trend in the number of CBE-0 supplements submitted. Further, without more historical context, it is possible that the number of submissions during the two-year period could be outliers—either abnormally high or low. Adding additional information concerning recent trends in the annual number of CBE-0 supplements is advised.

The PRIA assumes that all submitted information to the FDA webpage will be accurately posted, despite admitting that the possibility that errors and omissions in postings exist. While correcting incorrect information posted to the webpage is not likely to lead to substantial costs, such costs can be relatively easily estimated by accounting for industry averages or error rates observed in other areas of the FDA.

Lastly, the FDA discusses the possible costs associated with creating and maintaining the proposed FDA webpage. If additional resources are required, the "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.[12] However, these costs are not included in the low- and high-cost estimates for the proposed rule.

10. PRIA, 18.
11. Ibid.
12. PRIA, 17.

NO CONSIDERATION OF ALTERNATIVES

While this rule does not fall under the requirements of Executive Order 12866, the analysis would be improved, and the arguments more convincing, had the analysis followed the guidelines for regulatory planning and review set forth in the Executive Order. It states that "each agency shall identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees or marketable permits, or providing information upon which choices can be made by the public."[13]

Unfortunately, the PRIA for this regulation fails to consider any alternatives other than maintaining the status quo. The recommendation to adopt the proposed regulation would be much more convincing if a case could be made that the regulation addresses the public health concerns more effectively or at a lower cost than other reasonable alternatives.

CONCLUSION

For the reasons discussed above, the Food and Drug Administration presents an incomplete analysis of whether the "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products" regulation is in the best interest of society. No attempt is made to estimate the benefits of the regulation, and the analysis of the costs is very likely biased downward due to questionable assumptions and omissions. Further, changes of behavior are only selectively considered—discussing them when logically leading to benefits but dismissing the costs associated with those changes in behavior. A more complete analysis of both the costs and benefits is needed for the public and their elected officials to determine the true merits of this rule.

13. Exec. Order No. 12866, 58 Fed. Reg. 190 (October 4, 1993), 2.