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COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM  
MAJORITY STAFF REPORT  
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## **FDA CAREER STAFF OBJECTED TO AGENCY PREEMPTION POLICIES**

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PREPARED FOR  
CHAIRMAN HENRY A. WAXMAN

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## EXECUTIVE SUMMARY

Historically, the Food and Drug Administration (FDA) has viewed lawsuits brought by persons injured by a drug as a valuable complement to the agency's regulatory efforts. The longstanding view of the agency has been that private litigation can provide an additional layer of protection against unsafe drugs.

Under the Bush Administration, however, FDA has reversed this position and advocated in favor of preemption of individual state tort liability cases. FDA rewrote drug labeling regulations in 2006 and 2008 to restrict the ability of manufacturers to disclose new safety risks without prior FDA approval. The agency also added a lengthy preamble to the 2006 rule in favor of preemption of state lawsuits. The changes to the labeling rules (known as the "changes being effected" or CBE rules) and FDA's preamble have become a cornerstone of drug industry preemption arguments.

Internal agency documents obtained by the Committee show that these regulatory changes were made by FDA over the objections of key career officials. According to internal agency documents, high-ranking career officials repeatedly warned that the central factual justifications for the agency's new positions were false. They also expressed concern that the changes in the labeling rules would harm patients by significantly delaying the addition of important safety information to drug labels. These internal documents show that FDA career officials asserted that the regulations were based on a "false assumption," "naïve to what actually occurs in practice," relied on "gross overstatement," and made "false and misleading" assertions.

The preamble to the 2006 labeling rule asserted that FDA has the ability to "carefully control" drug labeling and to continuously monitor the safety of pharmaceutical products, incorporating information into the labeling when appropriate. Dr. John Jenkins, the highest official in FDA's new drug review process, strongly disagreed with these assertions, writing:

[M]uch of the argument for why we are proposing to invoke preemption seems to be based on a false assumption that the FDA approved labeling is fully accurate and up-to-date in a real time basis. We know that such an assumption is false.

He later amplified his objection, explaining: "we know that many current approved drug labels are out of date and in many cases contain incorrect information (e.g., the overdose section) ... [I]t is unwise to suggest that FDA approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information."

The preambles to both the 2006 and 2008 rules repeatedly state that without preemption and the new labeling restrictions, manufacturers will add unnecessary warnings. For example, the 2006 preamble asserts that state lawsuits "could encourage manufacturers to propose 'defensive labeling' to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments." This position was rejected by Jane Axelrad, Associate Director for Policy in the Center for Drug Evaluation and Research. She wrote to agency political appointees:

[T]here are continued references to sponsors “disclosing too much” risk information and its adverse impact. ... We rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors want to minimize the risk information.

She also asserted: “the statement that ‘FDA believes manufacturers should add risk information to labeling only after consulting with the agency ... is not true and is not consistent with our CBE regulations. ... [W]e do not discourage sponsors from adding new information. ... In fact, the regs encourage use of this route as it allows the label to be updated in the most timely manner.”

The preamble to the 2008 labeling rule claims that the revision merely conforms the language of the rule to the agency’s settled interpretation. Yet before the rule was issued, Ms. Axelrad advised that “[t]he rule is not, as it purports to be, consistent with the agency’s role in protecting the public health.” Ms. Axelrad also warned that, instead of reaffirming FDA’s long-standing interpretation, the 2008 rule created new standards that would create confusion:

We have not experienced problems with sponsors’ use of CBE supplements to over warn, and this rule tips the balance against early warnings by using vague and confusing terms such as “causal association” and “reasonable time” that will be difficult for staff and sponsors to apply.

At least one document suggests that the White House played a significant role in the preemption provisions and pressured the agency to reject the concerns of career experts. A senior career official wrote in 2006 that the FDA Chief Counsel “stated unequivocally that without the cbe language the rule will not go forward (this is per the White House).” Other documents reveal that after the changes went into effect, they delayed by months the addition of important safety information on drug labels.

FDA is charged with protecting public health by ensuring the safety and effectiveness of drugs and medical devices. But the documents received by the Committee call into question whether FDA has acted in the best interests of public health. The agency’s actions have undoubtedly helped shield drug manufacturers from liability. According to the agency’s own experts, however, they have done so at the cost of delaying the dissemination of important safety information to the public.

# I. INTRODUCTION

For over a century, state tort law has provided that Americans injured by a defective product can sue the manufacturer of that product for damages. This liability system has applied to FDA-regulated products since the FDA first began overseeing food and drug safety after the enactment of the Federal Food and Drugs Act of 1906. The only exceptions to the general rule of manufacturer liability involves childhood vaccines, which are subject to the Childhood Vaccine Injury Act of 1986,<sup>1</sup> and some bioterror countermeasures.<sup>2</sup>

FDA has historically viewed state lawsuits as providing a valuable complement to the agency's regulation of these products.<sup>3</sup> The agency has asserted that these cases help to uncover risks that are unknown to the agency at the time of approval and that they provide an important additional layer of consumer protection against unsafe products.<sup>4</sup> In 1997, former FDA Chief Counsel Margaret Jane Porter stated:

FDA's view is that FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection. FDA regulation of a device cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product such as a critical medical device may fail to identify potential problems presented by the product. Regulation cannot protect against all possible injuries that might result over time. Preemption of all such claims would result in the loss of a significant layer of consumer protection.<sup>5</sup>

At a recent hearing in the Committee on Oversight and Government Reform, former FDA Commissioner David Kessler and other witnesses testified that under previous administrations, FDA did not view the Federal Food, Drug, and Cosmetic Act (FDCA) as preempting state tort lawsuits.<sup>6</sup>

Under the Bush Administration, however, FDA's stance on the role of state tort liability changed dramatically. FDA issued two drug labeling rules containing provisions intended to reverse the agency's longstanding position that the agency's approval decisions did not preempt state tort actions. These rules are the 2006 Physician Labeling Rule and the 2008 revisions to the "Changes Being Effected" regulation.

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<sup>1</sup> Congress established the Vaccine Injury Compensation Program (VICP) with the passage of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-66. The VICP is a no-fault compensation program for people who have been injured by vaccines. Claimants go through a quasi-judicial process to determine if their injury was caused by a vaccine and, if so, how much compensation they should receive for their injuries. People seeking to sue a vaccine manufacturer in court must first go through the VICP.

<sup>2</sup> See, e.g., Homeland Security Act of 2002, Sec 304, Pub. L. No. 107-296.

<sup>3</sup> Dr. David Kessler and David Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, *The Georgetown Law Journal*, at 461, 463 (Jan. 2008). Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, *Food & Drug Law Journal*, at 7, 11 (Jan. 1997) (hereinafter "Porter").

<sup>4</sup> *Id.*

<sup>5</sup> Porter at 11.

<sup>6</sup> House Committee on Oversight and Government Reform, *Hearing on Should FDA Regulation Bar State Lawsuits?*, 110th Cong. (May 14, 2008).

## A. The 2006 Physician Labeling Rule

In January 2006, FDA issued a final drug labeling rule, commonly known as the “Physician Labeling Rule” (PLR).<sup>7</sup> The rule, which was the culmination of a major FDA initiative to make it easier for healthcare professionals to read and use drug labels, amended the content and format of prescribing information for human drug and biologic products.<sup>8</sup>

In the preamble to that rule, FDA announced a new view that the FDA-approved drug label preempts a sweeping range of traditional state actions related to drug labeling and advertising, including state product liability and medical malpractice cases.<sup>9</sup> Specifically, the preamble states that FDA believes that “under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law.”<sup>10</sup> FDA claimed in the preamble that its discussion of preemption responded to comments the agency received.<sup>11</sup> However, the preamble to the proposed rule, issued in 2000, specifically stated that the rule did not preempt state actions.<sup>12</sup> It also did not request comments on this conclusion.<sup>13</sup>

In addition to revising the content and layout of the labeling provided to healthcare professionals, the 2006 Physician Labeling Rule made revisions to FDA’s regulations governing how a manufacturer may add or change information on an approved drug label without first obtaining FDA approval. For decades, manufacturers were required to change their labels to add or strengthen a contraindication, warning, precaution, or adverse reaction without waiting for approval by the agency of such a change.<sup>14</sup> These regulations were known as the “changes being effected” or “CBE” regulations because they established a process by which a manufacturer could make immediate changes to the label, subject to revision after FDA completed its review of the changes and the data supporting them.<sup>15</sup> According to FDA officials, these regulations have helped ensure that patients and healthcare providers were made aware of safety risks associated with their medical products at the earliest possible moment.

The 2006 rule revised the CBE regulations to significantly restrict the authority of manufacturers to change drug labels. Specifically, the 2006 rule prohibited manufacturers from adding safety information or warnings to the new “highlights” section of a drug label without prior FDA

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<sup>7</sup> Food and Drug Administration, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922 (Jan. 24, 2006)(final rule) (hereinafter “2006 Physician Labeling Rule”).

<sup>8</sup> *Id.*

<sup>9</sup> *Id.* at 3933, 3935-6.

<sup>10</sup> *Id.* at 3934.

<sup>11</sup> *Id.* at 3933.

<sup>12</sup> Food and Drug Administration, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Prescription Drug Product Labels*, 65 Fed. Reg. 81082, 81103 (Dec. 22, 2000)(proposed rule).

<sup>13</sup> *Id.* at 81086. The proposed rule requested comment only on the issue of whether “the inclusion of a highlights section” would “have a significant effect on manufacturers’ product liability concerns,” i.e., whether the changes in the labeling rules would raise new products liability concerns.

<sup>14</sup> 21 CFR § 314.70, 21 CFR § 601.12, and 21 CFR § 814.39.

<sup>15</sup> *Id.*

approval.<sup>16</sup> The highlights section of a drug label is the first section of the label and contains “the information that healthcare professionals most commonly refer to and view as most important.”<sup>17</sup> The effect of the change is that any new safety information important enough to be included in the highlights section cannot be added by the manufacturer until FDA has completed its review process and approved the label changes.

The change in the authority of drug manufacturers to revise drug labels provided substantiation for the argument in the preamble that FDA approval of a drug label preempts state tort actions. The previous CBE rule had been a stumbling block to preemption claims because it preserved the responsibility of the manufacturer to revise the drug label to incorporate new information about safety risks. The revised CBE rule significantly curtailed manufacturer authority, bolstering FDA’s new assertion that the approved drug label could be regarded as a “ceiling” on permissible warnings in drug labels.

## **B. The 2008 “Changes being Effected” Regulation**

In August 2008, FDA issued a final rule further restricting a manufacturer’s ability to promptly add safety information to product labels in the absence of prior FDA approval.<sup>18</sup> This new rule amended the CBE regulations to prohibit a sponsor from adding or strengthening a contraindication, warning, precaution, or adverse reaction anywhere on the label unless it is based on “newly acquired information” and there is “sufficient evidence of a causal association with the drug, biologic, or medical device.”<sup>19</sup>

As in the case of the 2006 change, the change to the CBE regulation in 2008 further bolstered the FDA position that approval of drug label preempts state tort actions. In fact, immediately after the proposed rule was issued in January 2008, the Solicitor General sent a letter to the United States Supreme Court, supplementing its amicus briefs which argued that FDA approval of drugs and devices preempts state tort suits. The purpose of the letter was to notify the Court of the rule’s proposal because of its relevance to the preemption issue.<sup>20</sup>

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<sup>16</sup> 2006 Physician Labeling Rule at 3932, 3968-9.

<sup>17</sup> Food and Drug Administration, *FDA Announces the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products* (Jan. 18, 2006) (online at [www.fda.gov/cder/regulatory/physLabel/summary.htm](http://www.fda.gov/cder/regulatory/physLabel/summary.htm)).

<sup>18</sup> Food and Drug Administration, *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49603 (Aug. 22, 2008) (final rule) (hereinafter “2008 Changes Being Effected Supplement Rule”).

<sup>19</sup> *Id.* at 49604.

<sup>20</sup> Letter from Solicitor General Paul D. Clement to Honorable William K. Suter, Clerk, Supreme Court of the United States (Jan. 16, 2008). The Solicitor General’s letter was submitted with respect to the pending cases of *Riegel v. Medtronic, Inc.*, No. 06-179; *Warner-Lambers Co., LLC v. Kent*, No. 06-1498, *Wyeth v. Levine*, No. 06-1249.

## II. FDA INTERNAL DOCUMENTS

### A. Objections to the Discussion of Preemption in the 2006 Preamble

Documents provided to the Committee show that political appointees in FDA's Office of the Chief Counsel (OCC) authored and pressed for the inclusion of the preemption language contained in the preamble to the 2006 Physician's Labeling Rule. In so doing, the documents show, the Office of Chief Counsel ignored the warnings from FDA scientists and career officials that the preemption language was based on erroneous assertions about the ability of the drug approval process to ensure accurate and up-to-date drug labels.

In 2003, the Office of Chief Counsel circulated language inside FDA proposing that agency approval of a drug should preempt state lawsuits.<sup>21</sup> In response, Dr. John Jenkins, Director of the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER), provided comments to Jane Axelrad, Associate Director for Policy in CDER. On May 22, 2003, Dr. Jenkins wrote:

The premise of the basis for much of the argument for why we are proposing to invoke preemption seems to be based on a false assumption that the FDA approved labeling is fully accurate and up-to-date in a real time basis. We know that such an assumption is false. Even if the sponsor exercises due diligence to identify new risks after approval of a drug and submits requested changes in risk information to FDA in a timely manner, there will always be a delay before such information appears in the package insert, even in the case of a CBE supplement. So, it is unwise to suggest that FDA approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information. Even in the best case scenario of a diligent sponsor and a CBE supplement, the new risk information will not be available in the bottle or in printed materials like the PDR for some period of time.

In the background section of the document we argue "Manufacturer [sic] have product liability-related incentives to include exaggerated statements of risk information in labeling." I think this is a gross overstatement of the reality of what we see in working with sponsors regarding adding risk information to labeling. In my experience, the opposite is often the case; i.e., we more often find that sponsors disagree with our recommendations for how prominent warnings and precautions should be and suggest alternative language that lessens the impact of the warning.

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<sup>21</sup> The preemption language was initially part of a proposal by the Office of the Chief Counsel to reopen the comment period for Physician Labeling Rule, which was originally proposed in 2000. The 2000 proposed rule explicitly stated that it did not contain policies that preempted state law, and it did not request comments on preemption. Therefore, officials in the Office of Chief Counsel sought to reopen the comment period to solicit "comment on what actions, if any, the agency should take to clarify its views with respect to preemption of state common law and legislative requirements by federal law, to obviate the need for the agency to safeguard its role as the sole regulatory agency responsible for evaluating the safety, effectiveness, and labeling of prescription drugs through resource intensive case-by-case participation in judicial proceedings." Food and Drug Administration, *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Reopening of the Comment Period*, at 2 (draft proposed rule) (July 3, 2003). Ultimately, FDA did not reopen the comment period and never received public comment on the preemption language.

...The entire argument put forward that sponsors are insisting on exaggerated statements of risk information is naïve to what actually occurs in practice. While I do not believe that most sponsors deliberately attempt to obscure risk information about their products in the product labeling, I also believe it is true that sponsors attempt to present the information in a way that does not put their product at a competitive disadvantage to other products. ...

The discussion of CBE supplements for new safety information is not accurate. On page 8 it says that “If a manufacturer adds or strengthens a statement of risk information without at least consulting FDA in advance, it risks that they [sic] agency will disagree that the statement is appropriate. If FDA does disagree, the agency could initiate enforcement action on the ground that the labeling is false or misleading or fails to provide adequate directions for use. In practice, therefore, manufacturers do not exercise their entitlement to add risk information to labeling pending FDA’s evaluation of the change.” Each statement is misleading or incorrect. Sponsors sometimes discuss a CBE with us in advance, but that is far from the norm. We often review CBE supplements and decide that we think changes are warranted; rarely that the added statement is not appropriate. I don’t know of any example where we have taken enforcement action. Rather, we send the sponsor a letter either approving or not approving the change. In most cases we negotiate new wording that is then incorporated into the labeling.

On page 9 it says “FDA regulation of the dissemination of risk information in prescription drug and biological product labeling thus effectively operates as both a ‘floor’ and a ‘ceiling.’” I do not agree since sponsors can and do add new information without FDA prior approval.<sup>22</sup>

On June 18, 2003, Dr. Jenkins provided additional comments to Ms. Axelrad, writing:

I am not so comfortable with the whole argument in the document about preempting state liability cases against a manufacturer for “failure to warn” cases. I’m not sure why this falls within FDA’s purview (are there any other examples of where FDA has promulgated regulations based primarily on a desire to protect sponsors from liability?) and I think the whole argument that liability concerns drive inaccurate labeling is false and misleading. ... [T]he whole argument that liability concerns lead to decreased product innovation or product withdrawals is not supported by adequate data.<sup>23</sup>

Ms. Axelrad subsequently sent CDER’s collective comments in an edited version of the proposal to Chief Counsel Daniel Troy and Coleen Klasmeier, who was the Special Assistant to the Chief Counsel. In its edits, CDER repeatedly noted factual inaccuracies in the preemption argument. For

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<sup>22</sup> E-mail from Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), to Jane Axelrad, CDER Associate Director for Policy and Director, CDER’s Office of Regulatory Policy (May 22, 2003).

<sup>23</sup> E-mail from Dr. John Jenkins to Jane Axelrad, Dr. Janet Woodcock, then Director, CDER, and Dr. Steven Galson, then Deputy Director, CDER (June 18, 2003).

example, in response to an assertion that the threat of lawsuits could lead to unsubstantiated warnings, CDER wrote:

Our experience hasn't shown this. Companies rarely press for meaningful risk information or additional warnings. And they always oppose black box warnings. Much of the discussion of what goes in the label centers around the sponsors [sic] wish to promote the drug fully and to not be handicapped by risk information that would have to be conveyed in ads. Sponsors do seek to increase the reactions in the Adverse Reactions section because this influences their reporting requirements (if it's in the label, it is an expected event and reporting requirements are less).<sup>24</sup>

After receiving these comments, Daniel Troy circulated another draft dated July 3, 2003, to CDER officials seeking their comments. On August 6, 2003, Dr. Jenkins provided comments to Ms. Axelrad on the new draft, stating:

The draft makes reference to our “virtually plenary authority over drug labeling” and states that we “precisely control” the content and format of package inserts (see page 3). This seems to be a major overstatement of the facts and actual situation. While at a high level such statements may be true, we know that many current approved drug labels are out of date and in many cases contain incorrect information (e.g., the overdose section). Also, if we have so precisely controlled the content and format [sic] of drug labeling you have to wonder how we managed to develop a backlog of over 1000 labeling supplements during the same time that we were very focused on implementing the PDUFA goals. While we have eliminated that backlog, its mere existence for many years and the fact that we continue to go “overdue” on labeling supplements and to take up to 6 months to review even minor changes questions how “precisely” we perform this function. ...

On page 12 there is a statement that “Manufacturers generally consult FDA before adding risk information to labeling. ...” I don't know what this statement is based on and it is not in agreement with the large number of CBE labeling supplements to add risk information that we receive each year.<sup>25</sup>

On August 7, 2003, Ms. Axelrad sent CDER's collective comments on the draft circulated on July 30, 2003, to Mr. Troy and Ms. Klasmeier. CDER commented:

On page 4 and in other places there are continued references to sponsors “disclosing too much” risk information and its adverse impact on rational pharmacotherapy. Our concern is more that the risk information must be accurate and balanced. We rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors want to minimize the risk information. ...

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<sup>24</sup> CDER Redline of June 6, 2003 draft, at 46-7.

<sup>25</sup> E-mail from Dr. John Jenkins to Jane Axelrad, Dr. Robert Temple, Director, CDER's Office of Medical Policy, and Dr. Rachel Behrman, Deputy Director, CDER's Office of Medical Policy (Aug. 6, 2003).

On page 21 there is discussion of the Cardura case and the implication is that FDA is constantly monitoring the literature and that we force sponsors to add new risk information whenever we see a study that suggests one drug may be better than another. Nothing could be farther from the truth.

On page 23 there is the statement that “FDA believes manufacturers should add risk information to labeling only after consulting with the agency. ...” This is not true and is not consistent with our CBE regulations. Granted we review CBE supplements, but we do not discourage sponsors from adding new information via this route. In fact, the regs encourage use of this route as it allows the label to be updated in the most timely manner.<sup>26</sup>

On July 7, 2004, Dr. Steven Galson, the Acting Director of CDER, sent a memorandum to Mr. Troy containing CDER’s comments on the draft of the Physician Labeling Rule circulating at that time. Dr. Galson indicated that CDER objected to the inclusion of the preamble section on preemption because in CDER’s view “including such a section at this point in this rulemaking is likely to be quite controversial, and may make the rule vulnerable to legal challenge.”<sup>27</sup>

In August 2004, CDER and the Center for Biologics Evaluation and Research (CBER) reviewed drafts of the regulation. The routing slips indicate that both centers objected to the inclusion of the preamble language on preemption.<sup>28</sup>

The Office of Chief Counsel continued to work on subsequent drafts of the regulation throughout 2005. An e-mail from Dr. Rachel Behrman, Deputy Director of CDER’s Office of Medical Policy, indicates that the centers continued to be concerned about the inclusion of the preemption policy:

[T]he centers believe that an extensive discussion of preemption should not be included in this rule. The question of preemption is tangential to the purpose of this rule and any controversy that results from including it in the final rule may detract from the public health benefits that will be realized from revising prescription drug labeling. The working group believes that devoting twenty-five pages of text to explaining and defending preemption in a rule revising content and format of labeling is conspicuous and peculiar.<sup>29</sup>

The final Physician Labeling Rule was issued on January 24, 2006, with the preemption discussion opposed by the career officials. Despite the concerns of the career officials, the preamble to the final rule asserts that allowing state lawsuits “could encourage manufacturers to propose ‘defensive labeling’ to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.”<sup>30</sup> The final preamble also

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<sup>26</sup> E-mail from Jane Axelrad to Daniel Troy, Chief Counsel, Coleen Klasmeier, then Special Assistant to FDA Chief Counsel, Commissioner McClellan, Dr. Janet Woodcock, and Dr. Steven Galson (Aug. 7, 2003).

<sup>27</sup> Memorandum from Dr. Steven Galson, then Acting Director, CDER, to Daniel Troy (July 7, 2004).

<sup>28</sup> CDER Office of Regulatory Policy, Routing Slips (Aug. 6, 2004).

<sup>29</sup> E-mail from Dr. Rachel Behrman to Dr. Janet Woodcock, then FDA Deputy Commissioner for Operations and Chief Operating Officer, Dr. Jeff Shuren, Assistant Commissioner for Policy, Dr. Steven Galson, then Director, CDER et al. (Aug. 10, 2005).

<sup>30</sup> 2006 Physician Labeling Rule at 3935.

included other assertions contrary to the views of the career officials, including the assertions that FDA “carefully controls the content of labeling”;<sup>31</sup> that FDA continuously evaluates and monitors “the latest available scientific information” to “incorporate information into the product’s labeling”;<sup>32</sup> that FDA interprets the agency-approved language in a drug label as establishing “both a ‘floor’ and a ‘ceiling,’ such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading”;<sup>33</sup> and that “manufacturers typically consult with FDA” before making label changes.<sup>34</sup>

## B. Objections to the 2006 Drug Labeling Changes

E-mails from September 2005 between Seth Ray, an attorney in the Office of the Chief Counsel, and Sheldon Bradshaw, the Chief Counsel, indicate that Mr. Bradshaw asked Mr. Ray to investigate whether the draft final rule would permit a manufacturer to change the highlights section of a drug label without FDA approval.<sup>35</sup> Mr. Ray responded that he had looked through the rule and associated guidance and believed that Mr. Bradshaw’s question had not been addressed. Mr. Ray further asked whether “[i]n light of *Kallas*,” a case testing preemption of drug manufacturer liability, and “the preemption provision” contained in the preamble, “all or certain changes to highlights should not be permitted via CBE supplements?”<sup>36</sup> Mr. Ray added: “We would likely need to amend 314.70(c) in conjunction with the rule.”<sup>37</sup>

Mr. Bradshaw responded that changes to the highlights should not be permitted without prior FDA approval (“via CBE supplements”) and that the “reg should be changed.”<sup>38</sup>

On October 12, 2005, Dr. Rachel Behrman, Deputy Director of CDER’s Office of Medical Policy, indicated in an e-mail to Dr. Galson and Dr. Jenkins that the Office of the Chief Counsel had inquired about whether the highlights section could be changed without FDA approval. According to Dr. Behrman, “something about a current court case raised this in Sheldon’s mind.”<sup>39</sup>

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<sup>31</sup> *Id.* at 3934.

<sup>32</sup> *Id.*

<sup>33</sup> *Id.* at 3935.

<sup>34</sup> *Id.* at 3934.

<sup>35</sup> E-mail from Sheldon Bradshaw, then FDA Chief Counsel, to Seth Ray, Attorney, Office of the Chief Counsel, (Sept. 20, 2005).

<sup>36</sup> E-mail from Seth Ray to Sheldon Bradshaw (Sept. 20, 2005). On September 29, 2005, FDA filed an amicus brief on behalf of the defendant, Pfizer, in the case of *Kallas v. Pfizer*, Case No. 2:04CV0998 PGC, Utah District Court. In that brief, FDA argued that “a state tort law action against Pfizer for failing to depart from the FDA-approved labeling to add a warning of an association between Zoloft and adolescent suicidality/suicide is preempted.”

<sup>37</sup> E-mail from Seth Ray to Sheldon Bradshaw (Sept. 20, 2005).

<sup>38</sup> E-mail from Sheldon Bradshaw to Seth Ray (Sept. 20, 2005).

<sup>39</sup> E-mail from Dr. Rachel Behrman to Dr. Steven Galson, Dr. John Jenkins, and Dr. Robert Temple (Oct. 12, 2005).

A later e-mail from Mr. Ray provides further evidence that the provisions prohibiting changes to the highlights section without FDA approval came at the behest of Administration officials seeking to influence preemption litigation. Mr. Ray wrote:

[T]hese amendments were carefully crafted, in response to pending litigation, to ensure that changes to Highlights (other than minor changes) would only be made via prior approval supplements.<sup>40</sup>

Dr. Jenkins strongly disagreed with this proposal and questioned whether the policy was “consistent with our stated goal of getting new safety information out to doctors and patients quickly, even in cases where we (FDA) have not fully vetted the information.”<sup>41</sup> Dr. Jenkins further stated that the policy was “at odds with our focus on early notification of safety issues ... I’m surprised OCC does not have concerns about our restricting the sponsor’s ability to make timely changes to appropriately warn about new risks with their product.”<sup>42</sup>

Later e-mails indicate that Dr. Jenkins and other CDER officials continued to object to the highlights pre-approval policy but were ultimately overruled.<sup>43</sup>

### C. Resistance to a Proposal to Allow Waivers from Prior Approval Requirements

In early 2007, a year after publication of the final Physician Labeling Rule, CDER officials were encountering problems with the implementation of the pre-approval requirement for any change to the highlights section. According to internal e-mails, CDER officials were concerned that drug

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<sup>40</sup> E-mail from Seth Ray to Michael Bernstein, Director, CDER’s Division of Regulatory Policy II, Elizabeth Sadove, Regulatory Counsel, CDER’s Office of Regulatory Policy, Dr. Rachel Behrman, Sheldon Bradshaw et al. (Mar. 15, 2007).

<sup>41</sup> E-mail from Dr. John Jenkins to Dr. Rachel Behrman, Dr. Steven Galson et al. (Oct. 12, 2005).

<sup>42</sup> *Id.*

<sup>43</sup> *See, e.g.*, E-mail from John Jenkins to Jane Axelrad, et al. (Mar.29, 2007)(“This is not new of course since we had long discussions and specifically objected to this provision in the final PLR. We were over ruled.”); e-mail from John Jenkins to Jane Axelrad, et al. (Apr. 25, 2007) (“This is an important pathway to allow important new safety information to get to the labeling in a timely manner, and it is even more important today given our transmittal of new labeling to the NLM where it can be made available much more rapidly to prescribers and third party vendors. This is why most of our objected [sic] to the no CBE changes to the Highlights section of PLR and why we think it is important that we find a way to waive that requirement in appropriate cases.”)

Some career officials did support requiring FDA approval to make changes to the highlights section. E-mails from Dr. Rachel Behrman and Dr. Robert Temple to Dr. John Jenkins et al. (Oct. 12, 2005). Dr. Temple is head of the Office of Medical Policy, and, with respect to drug approvals, he also serves as Director of the Office of Drug Evaluation I, which is under the Office of New Drugs, headed by Dr. John Jenkins. E-mails from these officials on October 12, 2005, indicate that they believed that FDA could rapidly review prior approval supplements and that they could conduct a preliminary review then waive the prior approval requirement. As described in Section F of this report, the new prior approval requirement has significantly delayed addition of safety information to drug labels. In addition, for a long period, OCC refused to permit waivers of the prior approval requirement.

manufacturers were being prevented from adding important safety information to their product labels in a timely manner.<sup>44</sup>

To address this problem, a committee was formed within CDER to develop a waiver process that would allow manufacturers to bypass the highlights prior approval process when necessary to ensure prompt addition of new safety information. The committee formulated a proposal for establishing this waiver process and the proposal was presented to the Office of the Chief Counsel on January 23, 2007.<sup>45</sup> After having received no response from the Office of Chief Counsel, Elizabeth Sadove, a regulatory counsel at CDER, and Michael Bernstein, Director, CDER's Division of Regulatory Policy II, sent e-mails to Seth Ray urging the Office of the Chief Counsel to respond.<sup>46</sup> Finally, on March 15, 2007, Seth Ray responded in an e-mail:

I spoke with Sheldon [Bradshaw] and OCC does not concur with OND's draft procedure/policy document that would allow sponsors to request a waiver from the review division such that important safety labeling changes to Highlights could be made via CBE supplements. The draft document is inconsistent with the amendments made to 314.70 as part of the PLR. Some of you might not be aware that these amendments were carefully crafted, in response to pending litigation, to ensure that changes to Highlights (other than minor changes) would only be made via prior approval supplements.

Two weeks later, Dr. Jenkins sought Jane Axelrad's assistance to address the problem created by the highlights prior approval requirement:

Now we face the problem of how to get important new safety information into the labeling in a timely manner, which runs up against the PLR requirement for a prior approval supplement. ... Requiring a PAS [prior approval supplement] is really at odds with our goal to communicate safety information quickly and this is even more important as we are moving to the era of "real time" electronic labeling at NLM [the National Library of Medicine] (i.e., the labeling changes can now be an effective rapid communication tool). It is often difficult, if not impossible, for us to specifically agree to the sponsor's proposed changes since we need to review the data, which in some cases can be voluminous and may not be available for some time after the early signal is detected. ... The CBE mechanism provided the flexibility for us to provide some input and comment based on our preliminary review of the data while reserving our final decision on the appropriate labeling language until we completed our review. Help!<sup>47</sup>

A few weeks later, Ms. Axelrad spoke with Mr. Ray, who agreed to discuss this issue again with Chief Counsel Sheldon Bradshaw if Ms. Axelrad could supply "very specific and narrow criteria for

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<sup>44</sup> E-mail from Kim Colangelo, Associate Director for Regulatory Affairs, CDER's Office of New Drugs, to Dr. John Jenkins and Dr. Sandra Kweder, Deputy Director, CDER's Office of New Drugs (Mar. 29, 2007).

<sup>45</sup> E-mail from Elizabeth Sadove to Seth Ray (Jan. 23, 2007). Ms. Sadove wrote two follow-up e-mails to Mr. Ray (Feb. 12, 2007 and Mar. 8, 2007) after not receiving a response to her initial e-mail.

<sup>46</sup> E-mail from Elizabeth Sadove to Seth Ray (Mar. 8, 2007). E-mail from Michael Bernstein to Seth Ray (Mar. 8, 2007).

<sup>47</sup> E-mail from Dr. John Jenkins to Jane Axelrad, Dr. Sandra Kweder, Kim Colangelo, and Elizabeth Sadove (Mar. 29, 2007).

when a waiver would be applied.”<sup>48</sup> Ms. Axelrad then requested that CDER officials provide concrete examples of “safety changes that we thought were important that have been implemented through CBEs.”<sup>49</sup>

CDER staff identified several examples where prior review of the data might have caused a significant delay in updating the label because FDA needed additional time to make a final decision on the approved labeling. According to Dr. Jenkins, one example involved Vioxx:

When we met with Merck in September 2004 they had preliminary results of the APPROVE trial that showed an increased risk of CV events. Has [sic] Merck not decided to voluntarily withdraw the product it would have been necessary for them to make labeling changes since we would not have had access to the full study report for review so we could evaluate the actual data that would be added to the labeling. So, we probably would have agreed to interim labeling and asked Merck to submit it as a CBE and we would have made more official determinations later after we reviewed the full study report.<sup>50</sup>

Dr. Jenkins also described two examples where safety information gleaned from clinical trials was added to the label by the manufacturer without FDA prior approval:

The two attached examples ... are similar in that they led to addition of interim new important safety information the labeling, but without explicit FDA approval. ... While these two real world examples are related to new safety information from controlled trials, it is also possible that similar scenarios could arise from AERS [Adverse Event Reporting System] reports where we want to do a more comprehensive analysis and allow the sponsor to add changes via CBE in advance. ... This is an important pathway to allow important new safety information to get to the labeling in a timely manner, and it is even more important today given our transmittal of new labeling to the NLM where it can be made available much more rapidly to prescribers and third party vendors. This is why most of our [sic] objected to the no CBE changes to the Highlights section of PLR and why we think it is important that we find a way to waive that requirement in appropriate cases.<sup>51</sup>

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<sup>48</sup> E-mail from Elizabeth Sadove to Dr. John Jenkins, Dr. Sandra Kweder, Kim Colangelo, Michael Bernstein, Jane Axelrad, and Janet Norden, Associate Director for Regulatory Affairs, CDER’s Office of Medical Policy (Apr. 23, 2007).

<sup>49</sup> E-mail from Jane Axelrad to Elizabeth Sadove, Dr. John Jenkins et al. (Apr. 23, 2007).

<sup>50</sup> E-mail from John Jenkins to Jane Axelrad, Elizabeth Sadove, Sandra Kweder, Kim Colangelo, et al. (April 25, 2007). In the case of safety information that may emerge from a clinical trial, the agency typically relies on a full study report, which is a thorough presentation of data for the agency. This full compilation of the data can take the sponsor months — if not years — to compile. FDA can then take months more to fully analyze the data. In the context of Vytorin, Jenkins told the media that “the six-month time frame is our usual goal for completing a review of these types of submissions.” Food and Drug Administration, *Transcript of FDA Press conference on Early Communication about Ongoing Review of Vytorin* (Jan. 25, 2008) (online at [www.fda.gov/bbs/transcripts/2008/vytorin\\_transcript012508.pdf](http://www.fda.gov/bbs/transcripts/2008/vytorin_transcript012508.pdf)).

<sup>51</sup> E-mail from John Jenkins to Jane Axelrad, Elizabeth Sadove, Sandra Kweder, Kim Colangelo, et al. (Apr. 25, 2007).

One of the examples cited by Dr. Jenkins involves Proscar, a drug approved in 1992 to treat the symptoms of an enlarged prostate in men with benign prostatic hyperplasia. A large clinical trial in 2003 found more high-grade prostate cancers in patients taking Proscar as compared to patients not taking Proscar.<sup>52</sup> Based on this data, the manufacturer made a label change in September 2003, before the promulgation of the final Physician Labeling Rule.<sup>53</sup> FDA did not finish its review of the new information and approve the labeling change until April 23, 2004.<sup>54</sup>

The other example cited by Dr. Jenkins involved label changes for Zyvox, an antibiotic approved in 2000 to treat bacterial infections. A post-market clinical trial suggested that patients being treated for certain types of bloodstream infections were at higher risk for death when treated with Zyvox as compared to other antibiotics.<sup>55</sup> According to the medical reviewer in that case, “the change in the label (a CBE) was able to be made in about a week.”<sup>56</sup> This change was made before FDA had completed its review of the new data.<sup>57</sup> Like the Proscar change, this change was also not subject to the prior approval requirements of the 2006 rule.

In early August 2007, CDER officials were continuing to press for the establishment of a waiver process, but with little success.<sup>58</sup> At that time, political appointees in the Office of the Chief Counsel were working on drafts of the 2008 labeling regulation. CDER officials attempted to persuade the lawyers in the Office of the Chief Counsel to establish a waiver process within that rule, but were met with resistance.

As of December 2007, the issue remained unresolved. On December 17, 2007, Laurie Burke, Director of Study Endpoints and Labeling Development in the Office of New Drugs, wrote to Meredith Francis, regulatory counsel in CDER:

Several months ago, I heard that there were other CBE-related regs under development that trumped attention to this matter. We are still telling review divisions that a waiver is not an option and it’s their job to decide how to allocate their resources and prioritize these PASs (that have always been CBEs in the past) in

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<sup>52</sup> Dr. Ian Thompson et al., *The Influence of Finasteride on the Development of Prostate Cancer*, *New England Journal of Medicine* (Jul. 17, 2003).

<sup>53</sup> E-mail from Mark Hirsch, Medical Officer, Division of Reproductive and Urologic Drug Products, to Dr. John Jenkins (April 24, 2007).

<sup>54</sup> Letter from Daniel Shames, Director, Division of Reproductive and Urologic Drug Products, to Dr. Vivian Fuh, Merck & Company (Apr. 24, 2004) ([www.fda.gov/cder/foi/appletter/2004/20180slr029ltr.pdf](http://www.fda.gov/cder/foi/appletter/2004/20180slr029ltr.pdf)).

<sup>55</sup> Food and Drug Administration, *Linezolid (marketed as Zyvox) Information, FDA ALERT [3/16/2007]* (online at [www.fda.gov/cder/drug/infopage/linezolid/default.htm](http://www.fda.gov/cder/drug/infopage/linezolid/default.htm)).

<sup>56</sup> E-mail from Dr. Edward Cox, then Acting Director, Office of Antimicrobial Products, CDER’s Office of New Drugs, to Dr. John Jenkins, Dr. Sandra Kweder et al. (Apr. 24, 2007).

<sup>57</sup> E-mail from Dr. Edward Cox to Dr. John Jenkins, Dr. Sandra Kweder et al. (Apr. 24, 2007).

<sup>58</sup> E-mail from John Jenkins to CDER officials (Aug. 8, 2007) (“We had some discussions with OCC today about options regarding a waiver of the PLR requirement that all changes to the Highlights section be made via PAS. No decisions were made, but Jane and I made strong appeals that we find a way to address this issue as quickly as possible.”) E-mail from Laurie Burke, Director, Study Endpoints and Labeling Development, CDER’s Office of New Drugs, to Dr. John Jenkins, Kim Colangelo, Dr. Sandra Kweder, and Janet Norden (Aug. 9, 2007) (“In a meeting with OPS and Paula McKeever from Jane’s group about the 314.70 reg rewrite yesterday, we learned that OCC/Bradshaw is working on a change in those regs that will redefine CBE submissions and trump our initiative for the time being.”).

relation to all other pending work. As PLR labels become more prevalent and these types of PASs become more common, it would be good to have a final decision on the waiver option.<sup>59</sup>

The issue was ultimately clarified in a footnote to the proposed CBE rule in January 2008, and later in the preamble to the 2008 changes to the drug labeling rule.<sup>60</sup> The preamble indicated that FDA could waive the highlights limitation in appropriate circumstances.<sup>61</sup>

#### D. Objections to the 2008 Drug Labeling Changes

Officials in the Office of the Chief Counsel began work on additional revisions to the Changes Being Effected drug labeling rule in 2007. CDER officials first learned that Mr. Bradshaw, the Chief Counsel, was working on these changes at a meeting on August 8, 2007. According to an e-mail written the next day, CDER officials were notified that the changes “will redefine CBE submissions and trump our initiative [to establish a waiver process] for the time being.”<sup>62</sup>

An August 9, 2007, e-mail from Dr. Jenkins provides a glimpse into the rationale of the Office of the Chief Counsel:

OCC has a high priority rule in which they plan to add a couple of phrases to clarify what they view as our long standing intent for the CBE regulations for labeling changes. This is related to various litigations that are proceeding and may go to the Supreme Court. So, the goal for the publication of the PR [Proposed Rule] is late August with a final before the end of the year.<sup>63</sup>

On May 27, 2008, Gerald Masoudi, who replaced Mr. Bradshaw as Chief Counsel, sent a draft of the final rule to Ms. Axelrad. In forwarding the draft to other CDER officials, Ms. Axelrad wrote: “This is the rule that was done to shore up the agency’s arguments that we are preempting state tort law on failure to warn.”<sup>64</sup>

On June 17, 2008, Ms. Axelrad sent comments on a version of the draft final rule which she proposed to forward to the Office of the Chief Counsel to CDER officials, including Dr. Jenkins. She wrote:

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<sup>59</sup> E-mail from Laurie Burke to Meredith Francis, Regulatory Counsel, CDER’s Office of Regulatory Policy et al. (Dec. 17, 2007).

<sup>60</sup> Food and Drug Administration, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2850 (Jan. 16, 2008) (proposed rule).

<sup>61</sup> 2008 Changes Being Effected Supplement Rule at 49607.

<sup>62</sup> E-mail from Laurie Burke to Dr. John Jenkins, Kim Colangelo, Dr. Sandra Kweder, and Janet Norden (Aug. 9, 2007).

<sup>63</sup> E-mail from Dr. John Jenkins to Laurie Burke, Kim Colangelo, Dr. Sandra Kweder, and Janet Norden (Aug. 9, 2007).

<sup>64</sup> E-mail from Jane Axelrad to Dr. Robert Temple, Dr. Gerald Dal Pan, Director, CDER’s Office of Surveillance and Epidemiology, and Dr. John Jenkins (June 6, 2008).

The rule is not, as it purports to be, consistent with the agency's role in protecting the public health. We have not experienced problems with sponsors' use of CBE supplements to over warn, and this rule tips the balance against early warnings by using vague and confusing terms such as "causal association" and "reasonable time" that will be difficult for staff and sponsors to apply.

1. The rule will create confusion about the level of evidence needed to submit a CBE supplement and could discourage companies from quickly adding necessary warnings because of the confusion. The confusion arises because of the use of the term, "causal association" and the further references to 201.57(c)(6), which says that "causation need not have been definitively established." The rule is clearly trying to raise the bar on CBEs to support preemption, and references to 201.57 will not adequately prevent inappropriate reluctance on the part of sponsors to use a CBE supplement to add an important warning. The rule recognizes there may be some confusion by saying if there is doubt as to whether the standard of 201.57(c)(6) is met, the sponsor should confer with FDA. The rule doesn't say with whom sponsors should confer, or where the resources will come from to support such inquiries. Who does OCC believe will be answering those inquiries?
2. The distinction between whether the newly acquired information was submitted to the agency within a reasonable period of time prior to submission of a supplement creates a vague and unenforceable standard. Neither sponsors nor FDA staff will have any idea what "a reasonable time" means.
3. The rule on p. 4 says that "Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will ensure that scientifically accurate information appears in the approved labeling for such products." But there is no evidence that there is a need for any change to the rule or that without these vague and unenforceable standards scientifically inaccurate [sic] information has been appearing in the labeling.

Dr. Jenkins responded that he agreed with Ms. Axelrad's comments and thought it was good to get them on the record, writing: "In essence you are saying that we do not concur with the draft final rule, I wonder if you should be even more explicit in making that point."<sup>65</sup> Although the documents were not provided to the Committee, FDA has confirmed that Ms. Axelrad did forward those comments to officials in the Office of Chief Counsel.

#### **E. Evidence of White House and Department Interference**

FDA has informed the Committee that it has not yet produced a complete set of documents that would show communications between FDA officials and officials in the White House, the Department of Health and Human Services, and other agencies about the preemption and labeling

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<sup>65</sup> E-mail from Dr. John Jenkins to Jane Axelrad et al. (June 17, 2008).

changes. The documents that have been provided, however, suggest that officials in the White House and the Department threatened to block the Physician Labeling Rule, a major public health initiative on which FDA career officials had worked for many years, until the preemption changes were included. An October 28, 2005, e-mail from Rachel Behrman, Deputy Director of CDER's Office of Medical Policy, states: "We discussed the cbe issue with Sheldon [Bradshaw] who stated unequivocally that without the cbe language the rule will not go forward (this is per the White House)."<sup>66</sup> An August 9, 2007, e-mail from Dr. Jenkins indicates that there was also departmental pressure to make the labeling changes, stating that "the impetus ... came from the department."<sup>67</sup>

## F. Public Health Implications of the Changes

The documents provided to the Committee show that there have already been detrimental impacts from the 2006 rule requiring FDA approval before changes can be made to the highlights section of drug labels. In 2007, FDA received two requests from manufacturers seeking to immediately add safety information to their drug labels. Both requests concerned new risks that were so significant they needed to be included in the highlights section of the label. However, in both instances, the manufacturers were prohibited from promptly updating the drug label.

### 1. Delay in Tykerb Label Changes

Tykerb, manufactured by Glaxo Smith Kline, was approved by FDA on March 13, 2007, to treat certain forms of advanced breast cancer in combination with other cancer drugs.<sup>68</sup> Less than four months later, on May 22, 2007, a GSK representative wrote to FDA requesting permission to revise the approved labeling for the drug to include the additional adverse events of interstitial lung disease and pneumonitis, conditions characterized by abnormal growth of scar tissue in the lungs.<sup>69</sup> Because the damage is largely irreversible, interstitial lung disease and pneumonitis can lead to lifelong shortness of breath or even respiratory failure and death. The FDA-approved label for Tykerb did not mention the risk of interstitial lung disease when GSK submitted the request seeking to add that information.<sup>70</sup>

In his e-mail to FDA, the GSK official stated that "normally" the company would make an immediate label change "because the change would strengthen the warnings/precautions and lead to increased safe use of the drug."<sup>71</sup> However, the official noted that he was advised that "with the

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<sup>66</sup> E-mail from Dr. Rachel Behrman to Jane Axelrad, Dr. John Jenkins, and Dr. Steven Galson (Oct. 28, 2005).

<sup>67</sup> E-mail from Dr. John Jenkins to Laurie Burke et al. (Aug. 9, 2007).

<sup>68</sup> Food and Drug Administration, *FDA Approves Tykerb (lapatinib tablets) for Advanced Metastatic Breast Cancer Patients* (Mar. 2007) (online at [www.fda.gov/Cder/Offices/OODP/whatsnew/lapatinib.htm](http://www.fda.gov/Cder/Offices/OODP/whatsnew/lapatinib.htm)).

<sup>69</sup> E-mail from Dr. Richard Swenson, PhD, Senior Director, US Regulatory Affairs, GlaxoSmithKline, to Kim Robertson, Consumer Safety Officer, Office of Oncology Drug Products, CDER's Office of New Drugs (May 22, 2007).

<sup>70</sup> Food and Drug Administration, *Labeling Revision: Tykerb* (Apr. 27, 2007) (online at [www.fda.gov/cder/foi/label/2007/022059s001lbl.pdf](http://www.fda.gov/cder/foi/label/2007/022059s001lbl.pdf)).

<sup>71</sup> E-mail from Dr. Richard Swenson to Kim Robertson (May 22, 2007).

new labeling format (specifically the ‘Highlights’ section), we can no longer submit such a change as a CBE supplement if it impacts the ‘Highlights’ section.”<sup>72</sup>

E-mails reveal that GSK refrained from adding the information about the risk of developing interstitial lung disease and pneumonitis to the label. Instead, the company prepared a prior approval supplement, which it filed with FDA on July 25, 2007, over two months after the company initially requested to add the safety information to the drug label.<sup>73</sup> GSK requested that FDA review the supplement within three days, but FDA was unable to do so. It was not until August 20, 2007, three months after the company first approached FDA with the proposed labeling change, that FDA approved the labeling change to incorporate the new safety information into the label.<sup>74</sup>

## 2. Delay in Levaquin Label Changes

Levaquin, manufactured by Johnson and Johnson (J&J), was approved by FDA on December 20, 1996, as an antibiotic in the quinolone class. In June 2007, FDA required the entire class of quinolones to include on each label a warning about the risk for liver damage.<sup>75</sup> According to an internal FDA e-mail, J&J apparently further examined the risk for liver damage and, based on its findings, wanted to strengthen the warning in the label. In November 2007, J&J submitted a supplement to strengthen the warnings pertaining to liver toxicity related to the use of the drug.<sup>76</sup>

According to internal documents provided to the Committee, in the acknowledgement letter to this supplement, FDA stated “changes of this kind cannot be put into effect according to the Physician Labeling Rule regulations that state that the HIGHLIGHTS section of the package insert cannot be modified prior to approval of the supplements. Approved supplements are required for this proposed change prior to distributing drug products made with this change.”<sup>77</sup> FDA noted that it would take some time for the agency “to review and approve” the changes, but FDA was “trying to finish the review by the end of the month.”<sup>78</sup> Internal documents show that FDA apparently granted J&J a waiver of the preapproval requirement, and the company added information about hepatotoxicity in February 2008, a delay of three months.<sup>79</sup> According to FDA’s website, however, FDA did not approve the strengthened warning until April 16, 2008.<sup>80</sup> When the new label was

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<sup>72</sup> *Id.*

<sup>73</sup> Letter from Richard Swenson to Dr. Robert Justice, Director, Division of Drug Oncology Products, CDER’s Office of New Drugs (July 25, 2007).

<sup>74</sup> Letter from Dr. Robert Justice to Dr. Richard Swenson (Aug. 20, 2007) (online at [www.fda.gov/cder/foi/appletter/2007/022059s002ltr.pdf](http://www.fda.gov/cder/foi/appletter/2007/022059s002ltr.pdf)).

<sup>75</sup> E-mail from Dr. Rebecca Saville (PharmD), Regulatory Project Manager, Division of Special Pathogens and Transplant Products, CDER’s Office of New Drugs, to David Roeder, Associate Director for Regulatory Affairs, Office of Antimicrobial Products, CDER’s Office of New Drugs (Jan. 3, 2008).

<sup>76</sup> E-mail from Dr. Rebecca Saville to David L. Roeder (Jan. 3, 2008).

<sup>77</sup> E-mail from Dr. Renata Albrecht, Director, Division of Special Pathogen and Transplant Products, CDER, to Dr. John Jenkins et al. (Jan. 7, 2008).

<sup>78</sup> E-mail from Dr. Rebecca Saville to David L. Roeder (Jan. 3, 2008).

<sup>79</sup> E-mail from Rebecca Saville to Diana Williard (Feb. 6, 2008).

<sup>80</sup> Letter from Dr. Renata Albrecht to Alysia Baldwin-Ferro, Senior Director, Regulatory Affairs, Johnson and Johnson (Apr. 16, 2008) (online at: [www.fda.gov/cder/foi/appletter/2008/020634s051,%20020635s055,%20021721s019ltr.pdf](http://www.fda.gov/cder/foi/appletter/2008/020634s051,%20020635s055,%20021721s019ltr.pdf)).

finally approved, it added the following warning: “severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur.”<sup>81</sup>

### III. CONCLUSION

Internal FDA documents provided to the Committee reveal that in 2006 and 2008, FDA promulgated drug labeling regulations that contradicted the advice of FDA’s high-ranking career officials. Publicly, FDA justified its preemption policies on the grounds that state lawsuits “could encourage manufacturers to propose ‘defensive labeling’ ... [and] scientifically unsubstantiated warnings.” But, internally, senior FDA officials wrote that “[w]e rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary”; that “[t]he entire argument ... that sponsors are insisting on exaggerated statements of risk is naïve to what actually occurs”; and that “the whole argument that liability concerns drive inaccurate labeling is false and misleading.” They also stated that it was “unwise to suggest that FDA approved labeling is always up-to-date,” and that the requirement of prior FDA approval for labeling changes was “not consistent with agency’s role in protecting the public health” and created “the problem of how to get important new safety information into the labeling in a timely manner.”

FDA has an obligation to ensure the safety and effectiveness of drugs. In this case, however, the internal documents indicate that the Bush Administration weakened important drug safety regulations to shield manufacturers from liability. That is a serious abuse of the agency’s public health authorities.

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<sup>81</sup> Food and Drug Administration, *Labeling Revision: Levaquin* (Oct. 3, 2008) (online at [www.fda.gov/cder/foi/label/2008/021721s020\\_020635s57\\_020634s52\\_lbl.pdf](http://www.fda.gov/cder/foi/label/2008/021721s020_020635s57_020634s52_lbl.pdf)).