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March 22, 2006

Andrew von Eschenbach, M.D.  
Acting Commissioner of Food and Drugs  
Food and Drug Administration  
Division of Dockets Management (HFA-305)  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

### Citizen Petition

Dear Commissioner:

Wyeth, by its counsel, submits this petition pursuant to 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs withdraw a Notice of Proposed Rulemaking ("NPRM"), issued by the Food and Drug Administration ("FDA") on December 22, 2005, to reclassify over-the-counter ("OTC") nasal decongestant and weight control drug products containing phenylpropanolamine ("PPA") from their previously proposed monograph status (Category I) for these uses to nonmonograph (Category II) status.<sup>1</sup> Wyeth is a former manufacturer of products that contained PPA. Although Wyeth no longer markets such products, and has no intent to do so in the future, the company is a defendant in product liability lawsuits concerning products that once contained PPA. Plaintiffs may attempt to use FDA's statements in the preamble to the NPRM as evidence in these cases. Thus, Wyeth has an interest in assuring the accuracy of FDA's statements.

#### A. Action Requested

Wyeth requests that the Commissioner withdraw the NPRM. It contains statements of material fact that are inaccurate and misleading to the public. Moreover, the agency would have known that at least some of these statements were erroneous if it had reviewed information in its possession or available in the medical literature. As to other statements, Wyeth is submitting documentation to demonstrate that these too are misinformed and unreliable.

In order to present the public with a fully-informed and well-considered proposal regarding the safety of PPA, FDA should withdraw the present NPRM, reconsider it in light of the information presented by Wyeth, and, if appropriate, publish a new proposal. The requested withdrawal would not prejudice any subsequent agency action.

<sup>1</sup> 70 Fed. Reg. 75,988 (December 22, 2005) (relating to FDA Docket Nos. 1976N-0052N and 1981N-0022).

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**B. Statement of Grounds**

Wyeth refers FDA to, and incorporates by reference, its response to FDA's NPRM, which Wyeth has submitted separately on March 22, 2006.<sup>2</sup> In its submission, Wyeth demonstrates that:

- **the NPRM assumes the reliability of the Hemorrhagic Stroke Project ("HSP"), a study that is now known (through information not previously available to FDA) to have been irreparably compromised;**
- **the NPRM omits crucial information known or reasonably knowable to FDA; and**
- **in light of this information, the NPRM misstates material facts and misleads the public.**

The Administrative Procedure Act ("APA") and FDA's own regulations, as well as fundamental fairness, require the agency to consider and assess all relevant factors bearing on the safety of PPA, and provide the public with an accurate and complete statement of the reasons for the proposed action.<sup>3</sup> Only by having an adequate and non-misleading analysis of the facts on which FDA relies can the public intelligently comment. It defeats the entire process for an agency to misrepresent the facts before it, in order to justify the action being proposed.

In this case, FDA has incorrectly described scientific studies relied upon to justify its proposal. Moreover, the agency has failed to disclose the existence of other, indisputably relevant data that are in the public domain, both in published medical literature and in comments submitted to FDA in related proceedings. Finally, the NPRM indicates, both by what it says and by what it does not, that FDA has not been made aware of important information about the HSP that was obtained during product liability litigation through subpoenas to, and depositions of, the HSP investigators and others sources.

FDA is legally required to consider this information, which directly contradicts numerous statements made in the NPRM, before it makes its proposal. It cannot rely on the notice-and-comment process to correct the misleading information contained in the NPRM.

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<sup>2</sup> See Attachment 1. This attachment contains the text of the comments, without the voluminous supporting documentation, which is available in the docket of the NPRM.

<sup>3</sup> See 21 C.F.R. § 10.40(b)(vii).

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## I. Injury to Public: Deprivation of Open and Transparent Administrative Process

Under the APA, a federal agency is under an obligation to consider “relevant data and articulate a satisfactory explanation of its action, including a ‘rational connection between the facts and the choice made.’”<sup>4</sup> A reviewing court will consider “an agency rule [to] be arbitrary and capricious if the agency . . . entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference of view or the product of agency expertise.”<sup>5</sup> A leading case on the issue reiterates this premise, stating, “It is not consonant with the purpose of a rule-making proceeding to promulgate rules on the basis of inadequate data.”<sup>6</sup> Consequently, a reviewing court must “assure itself that all relevant factors have been considered by the agency.”<sup>7</sup>

Furthermore, informal rulemaking requires an “exchange of views, information and criticism between interested persons and agency” which means that the agency “must disclose in detail the thinking that has animated the form of proposed rule and data upon which it was based.”<sup>8</sup> In this process, an agency is entitled to make choices and judgments, but they must be based on facts and reflect the analysis of the agency -- and they must be presented in the notice of proposed rulemaking.

[The APA’s n]otice requirements are designed (1) to ensure that agency regulations are tested via exposure to diverse public comment, (2) to ensure fairness to affected parties, and (3) to give affected parties an opportunity to develop evidence in the record to support their objections to the rule and thereby enhance the quality of judicial review.<sup>9</sup>

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<sup>4</sup> *Motor Vehicle Manufacturers Association v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29, 43 (1983) (describing what is now generally considered the *State Farm* “hard look”) (internal citations omitted).

<sup>5</sup> *Id.*

<sup>6</sup> *Portland Cement Ass’n v. Ruckelshaus*, 486 F.2d 375, 393 (D.C. Cir. 1973).

<sup>7</sup> *Home Box Office, Inc. v. F.C.C.*, 567 F.2d 9, 36 (D.C. Cir. 1977) (internal citations omitted).

<sup>8</sup> *Id.* at 35.

<sup>9</sup> *International Union, United Mine Workers of America v. Mine Safety & Health Administration*, 407 F.3d 1250, 1259 (D.C. Cir. 2005) (citing *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506 (D.C. Cir. 1983)).

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Recently, the U.S. Court of Appeals for the District of Columbia Circuit set aside a final rule of the Environmental Protection Agency as unlawful because it failed to disclose in the notice of proposed rulemaking that it might take the action it ultimately chose. The Court observed that “we have refused to allow agencies to use the rulemaking process to pull a surprise switcheroo on regulated entities.”<sup>10</sup> In short, “there must be a dialogue between public and agency because the opportunity to comment is meaningless unless agency responds to significant points raised by public.”<sup>11</sup> It is equally meaningless if the agency misstates or misrepresents critical facts on which it relies, for the public may be trusting in the integrity of the government and accept the misstatements as gospel.

In this situation, FDA dusted off a notice of opportunity for a hearing (NOOH) on the proposed withdrawal of new drug applications for products containing PPA that was published in 2001.<sup>12</sup> It barely made any changes in the text of the notice, other than cosmetic alteration.<sup>13</sup> Because FDA appears to have based the 2001 NOOH on exactly the same data and reasoning as the 2005 NPRM, a meaningful dialogue between FDA and the public requires that the agency respond to the important comments it received on the NOOH. In 2001, Wyeth advised FDA, “Significant differences exist in the conclusions reached in the [unpublished HSP] Final Report [cited in the NOOH] and the later published version” of the HSP.<sup>14</sup> Wyeth provided specific examples of the differences.<sup>15</sup> Although FDA cited the published report elsewhere in the NPRM,<sup>16</sup> and was on notice that the published report differed from the unpublished report, the agency nevertheless referenced exclusively to the unpublished report in its analysis of the data on the safety of PPA. In the critical part of the NPRM, the agency did not mention the published report, let alone identify the differences between it and the unpublished version or explain the reasons why FDA chose to rely on the unpublished HSP report over the published version. Instead, as shown in Appendix 2, the agency merely repeated the contents of its 2001 NOOH.

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<sup>10</sup> *Environmental Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005).

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

<sup>12</sup> 66 Fed. Reg. 42,665 (Aug. 14, 2001).

<sup>13</sup> See Attachment 2 (a side-by-side textual comparison of the 2001 NOOH with the 2005 NPRM). 

<sup>14</sup> Wyeth Comments, dated September 21, 2001, FDA Docket No. 01N-196, C4.

<sup>15</sup> *Id.* at 4-6.

<sup>16</sup> See 70 Fed. Reg. at 75,996 (col.1) and Ref. 14.

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The NPRM also ignores subsequent publications analyzing subsets of the HSP data, as shown in Wyeth's comments on the NPRM.<sup>17</sup> Further, it fails to discuss the agency's previous assessments of data on blood pressure effects of PPA.<sup>18</sup> The public is left in the dark about the very existence of these other sources of information bearing on the substance of FDA's proposal. It is denied a meaningful opportunity to comment because it is unaware of these issues.

Moreover, the public is deprived of FDA's position on other facts that are now known about the validity of the HSP study. A citizen might rightfully assume that FDA was on top of the subject, not locked in a time capsule dated "October 2000" and ignoring any publications or comments occurring after that time. Without careful study of the material not discussed by FDA, she or he might defer to the agency's conclusions, without realizing how flawed they are. In a perfect world, of course, the ideal citizen might read the comments received, such as those submitted by Wyeth, and realize how incomplete and misleading FDA's analysis was. But Wyeth's comments will not be published in the *Federal Register* and will not be easily available. As a result, the ordinary citizen is deprived of both a well-considered appraisal by FDA of all of the evidence available to the agency and also a meaningful opportunity to participate in the rulemaking process.

The remedy for this situation is for FDA to withdraw the current NPRM, on the ground that the agency had not yet considered crucial information bearing on the safety of PPA that was in the agency's possession. This action would not prejudice FDA from issuing any new proposal it felt justified, based on the totality of the record before it.

This step would also provide FDA with an extraordinary opportunity. Unlike most situations, the agency now has available to it detailed supplemental information regarding the HSP from its investigators that was developed in a lengthy litigation discovery and fact-finding process. In its comments, Wyeth is submitting HSP records that may not have previously been known to the agency, as well as sworn statements of the HSP investigators obtained in depositions. Rarely has the agency had such a thorough and complete record relating to a study on which it has placed so much reliance. Withdrawal of the present NPRM to consider the information that was available to FDA prior to December 2005 will permit the agency to consider this additional information as well.

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<sup>17</sup> See Attachment 1, at 19-20.

<sup>18</sup> See Attachment 1, at 20-21.

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## II. Injury to Wyeth and Other Manufacturers of PPA-Containing Products

Wyeth is a former manufacturer of products containing PPA. It is engaged as a defendant in multiple product liability cases involving PPA, as are other former manufacturers.

The preamble in the NPRM may adversely affect Wyeth if courts erroneously conclude that the preamble is an "advisory opinion" that represents "the formal position of FDA" on the safety of PPA, based on a simplistic reading of the agency's regulations.<sup>19</sup> This interpretation would not be consistent with these regulations, however, which make clear that advisory opinions only address a "policy issue of broad application" and would not purport to cover "a particular product or ingredient" such as PPA.<sup>20</sup> Moreover, an advisory opinion obligates the agency only to adhere to the policy until changed.<sup>21</sup> In this case, the NPRM reaches only "tentative conclusions," based on a preliminary analysis of the data which the public is invited to correct. FDA cannot be said to have bound itself to any specific outcome of the proposal. Indeed, the notice-and-comment rulemaking process only works if the agency is not obligated to a particular result.

Nevertheless, Wyeth and other defendants may be required to argue this proposition in numerous courts -- without certainty of success. This challenge is not new. When the NOOH was issued, Wyeth asked that FDA clarify that statements made in an NOOH are not findings after an adjudication through an evidentiary hearing on the merits. Wyeth expressed the concern that plaintiffs would likely attempt to use FDA's statements in the NOOH as evidence in product liability cases involving PPA. Further, in responding to any challenges companies may raise to the HSP in the courts, plaintiffs would argue that the NOOH should be read as endorsing the HSP or definitively interpreting its results. FDA took no action, and Wyeth's concerns were realized. The NOOH has been used against Wyeth in numerous proceedings.

Accordingly, Wyeth believes that it faces the risk of further injury if courts misinterpret the preamble as an expert assessment of all available information, when in fact it is an appraisal of a small portion of the currently available information. The only way FDA can prevent this misunderstanding is to withdraw the NPRM because it did not reflect a review of all available information. Such an action would not prejudice FDA's ability to issue a new proposal in the future, after it has considered the information before it.

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<sup>19</sup> See 21 C.F.R. § 10.85(d), (e).

<sup>20</sup> See 21 C.F.R. § 10.85(a)(iv).

<sup>21</sup> See 21 C.F.R. § 10.85(e).

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## C. Environmental Impact

The NPRM states that the agency has determined that the action proposed is of a type that does not individually or cumulatively have a significant effect on the human environment and, therefore, neither an environmental assessment ("EA") nor an environmental impact statement ("EIS") is required.<sup>22</sup> The withdrawal of the NPRM should thus have no significant effect either, and petitioner claims a categorical exclusion from the requirement to submit either an EA or an EIS.

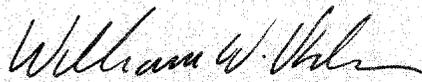
## D. Economic Impact

The NPRM presents a deeply flawed economic impact assessment regarding the proposed action.<sup>23</sup> Wyeth addressed the economic analysis in its comments.<sup>24</sup> Wyeth will not submit any further information in connection with this petition unless required by FDA.

## E. Certification

The undersigned certifies that, to the best knowledge and belief of Wyeth, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Arnold & Porter LLP  
Counsel for Wyeth

By:   
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William W. Vodra

cc: Madeline Stoller, Esq.  
Wyeth

Stephen A. Cooper, D.M.D., Ph.D.

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<sup>22</sup> 70 Fed. Reg. at 75,996 (col. 3).

<sup>23</sup> 70 Fed. Reg. at 75,994-96.

<sup>24</sup> See Attachment 1, page 26.