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September 20, 2006

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Congressman Mike Ferguson
House of Representatives
Congress of the United States
214 Cannon House Office Building
Washington, D.C. 20515

Dear Congressman Ferguson:

In response to your inquiry dated September 6, 2006 addressed to Mr. John Bonitt, I am responding to you on behalf of Eli Lilly and Company (Lilly). You requested information about the following topics:

- Lilly's policies regarding the issuance of Medication Guides,
- Lilly's role in ensuring the distribution of Medication Guides, and
- Lilly reviews that are being conducted to ensure distribution of Medication Guides in compliance with federal regulations.

Lilly shares your belief that Medication Guides are a vital communication tool. This information is needed to enable informed decisions about the use of antidepressant medications. In addition to the four Lilly products that require an antidepressant Medication Guide, Lilly has two other products for which Medication Guides are required. In the following pages, you will find information responding to your inquiry that outlines the responsibilities of the manufacturers of drugs required to have Medication Guides and what policies are in place at Lilly to ensure compliance with these regulations. We also outline actions we take to monitor Lilly's compliance to these regulations and have provided comments (per your request) on what we see as Best Practices.

Regulatory Requirements:

According to 21 Code of Federal Regulations (CFR) 208, Medication Guides are patient labeling intended for outpatient products that pose a "serious and significant public health concern." The Food and Drug Administration (FDA) may require a Medication Guide if it could help prevent serious adverse effects, if there are serious risks that may affect a patient's decision to use or continue use of a product, or if patient adherence to directions is crucial to the drug's effectiveness. If a Medication Guide is required, pharmaceutical manufacturers must ensure these agency-approved patient labeling documents are available for distribution by either providing enough to dispensers to give one to each

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patient or provide "means to produce" enough for each patient. It is important to note that authorized dispensers include pharmacists and other healthcare professionals who provide drug products directly to patients. In addition, manufacturers must ensure that the label of each container or package includes prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. Distributors or wholesalers must pass on Medication Guides received from sponsors (i.e., Lilly) to dispensers. Then, "each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each patient (or to the patient's agent) unless an exemption applies under 208.26."

Lilly's Policies on the Creation, Printing, Packaging and Distribution of Medication Guides:

Policies and procedures are corporate documents that define and control how work activities are completed. These documents are approved by management, reviewed and updated (as needed) on a regular schedule. Compliance is expected of all employees whose work is governed by these specific documents. The following polices govern the creation, printing, and packaging of US labeling documents, which include the US Package Inserts, Patient Package Inserts, and Medication Guides. (It is important to note that each involved Lilly functional area and manufacturing site has local procedures to supplement these policies.)

- Policy for US Pharmaceutical Labeling
- Printed Packaging Material Management for Finished Product
- Packaging Operations for Finished Product

According to Lilly's policy for labeling, US labeling (including Medication Guides) must comply with US regulations, US FDA requirements and Lilly corporate labeling policies. The Global Operations Labeling Department (GOLD) at Lilly facilitates the process of developing US labeling content, and then they work with the US Regulatory Affairs department at Lilly to identify reviewers and approvers per Lilly's process for the internal review and approval of US labeling documents. *Reviewers* are responsible for ensuring the accuracy of the information contained in US labeling that is within their areas of expertise. *Approvers* are accountable for confirming that the US labeling has been reviewed for technical accuracy and completeness. *Approvers* have corporate accountability for US labeling documents. GOLD is responsible for maintaining the content and managing version control of US labeling text; therefore, GOLD serves as the central repository from which all other departments must obtain labeling text.

Preparation of printed materials is completed per procedures for the US Printed Packaging Materials Development area based on content obtained from GOLD. Initiation of this process is based on a request from GOLD. The printed piece will be processed through our graphics and proofreading process. This proof copy will then be forwarded back to GOLD to be reviewed and approved prior to final printing and distribution.

Packaging of Medication Guides is processed similarly to all other printed materials including inserts, labels, and cartons. They are physically attached to or included with the product and handled using the same quality systems and procedures. These efforts ensure that the right printed packaging material is provided together with the product on the packaging line.

Packaged *trade* drug product that has been created via these processes containing the required Medication Guides is provided to wholesalers and distributors to be passed along to the ultimate dispensers. Packaged *sample* drug product containing required Medication Guides is provided by company sales representatives to healthcare professionals authorized to prescribe. These efforts ensure that we meet regulatory authority requirements for pharmaceutical manufacturers.

Lilly's Role in the Creation and Implementation of the Antidepressant Medication Guide:

With respect to the specific antidepressant Medication Guide, Lilly maintained close interactions with the FDA during the implementation of the boxed warning labeling and Medication Guide for all of our products. We made numerous regulatory submissions of our planned actions for both the labeling and Medication Guides from the receipt of their request on October 15, 2004 through FDA approval of the labeling and Medication Guide on February 18, 2005. In addition, Lilly actively participated in a working group that was composed of FDA officials, pharmaceutical companies, state boards of pharmacy and retail pharmacies, publishers of patient information materials and patient education organizations. This working group was organized to implement a unified and standardized procedure for providing Medication Guides to patients receiving antidepressant medications. A temporary procedure was initially put in place to provide pharmacies with bulk tear-off copies of the Medication Guides. This temporary procedure has subsequently been replaced by each manufacturer's process for distributing Medication Guides. Lilly fully complied with the official FDA request as well as the agreed upon procedures from the Medication Guide working group.

Lilly Reviews via Monitoring and Audits:

All areas involved in the creation, printing, packaging, and distribution of US labeling, including Medication Guides, have monitoring and auditing plans in place to ensure

compliance with area policies and procedures. In the US, Lilly provides a central call center to which healthcare professional and patient questions and concerns (e.g., requests for Medication Guides) can be directed. Complaints from customers regarding these or other matters are forwarded to the appropriate technical areas for investigations, as appropriate.

Best Practices:

In our review of current Lilly practices, we identified a number of approaches that appear to offer significant advantage over other possible methods that could have been selected. A few of these observations are briefly described below:

- Printing of the Medication Guides as a separate and distinct document from the package insert allows for easy distribution by the dispenser to the patient.
- Medication Guides are packaged with or affixed to each individual bottle or multi-count bottles of medication, eliminating the need for wholesalers and distributors to take any special actions to ensure that the Medication Guides are delivered to dispensers (i.e., these bottles move through the supply chain in the same manner as those not required to carry Medication Guides.)
- Medication Guides are made available on product websites for easy access by healthcare professionals and patients.

We trust that you will find the information provided in this letter to be useful as you work to understand the genesis of the concerns reported to you by some of your constituents. Should you have additional questions regarding this matter, do not hesitate to contact me at (317) 277-1324.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Vice President
Global Regulatory Affairs