MEMORANDUM OF AGREEMENT BETWEEN
THE OFFICE OF NEW DRUGS
AND
THE OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
IN THE CENTER FOR DRUG EVALUATION AND RESEARCH

I. INTRODUCTION

This document outlines an agreement between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) in the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) on the management of significant safety issues associated with pending and approved drug products.

A significant safety issue for purposes of this memorandum of agreement is a safety issue that has the potential to lead to, for example:

- withdrawal of an approved drug from the market;
- withdrawal of an approved indication;
- limitations on a use in a specific population or subpopulation in the post-marketing setting;
- changes to the warnings, precautions, or contraindication sections of the labeling (including the addition of a boxed warning to the label);
- the establishment of, or changes to, the proprietary name/container label/labeling/packaging to reduce the likelihood of medication errors;
- the establishment or modification of a risk evaluation and mitigation strategy (REMS);
- addition or modification of a Medication Guide or other required Patient Package Insert that addresses a safety issue;
- the requirement that a sponsor conduct a post-marketing clinical trial; or
- the conduct of an observational epidemiological study by the sponsor or FDA.

Significant safety issues affecting unapproved marketed products will be addressed under separate procedures.

This document clarifies the roles and responsibilities of OND and OSE in implementing CDER's policies that 1) the resolution of significant safety issues that arise concerning drug products must be given the highest priority in the Center and 2) OND and OSE views are to be given equal weight in determining how significant safety issues affecting drug products are resolved.

Reviews of applications and supplements have long relied upon a multidisciplinary team-based approach. OSE has traditionally been consulted by OND or other program offices through a formal consultative process when safety issues arise pre- or post-market, but the responsibility for decision-making has rested within OND. Under this agreement,

significant safety issues will be managed by interdisciplinary teams and OND and OSE will have equal responsibility for the resolution of significant safety issues and determining appropriate regulatory action.

This agreement also designates OSE as the scientific lead and review team lead for certain pre- and post-market regulatory actions and outlines the intent for OSE to assume certain signatory/regulatory authorities in these areas and potentially others in the future.

Finally, this agreement assists FDA in implementing the Food and Drug Administration Amendments Act of 2007 (FDAAA) by clarifying program responsibilities associated with implementing the FDAAA provisions regarding postmarketing study and clinical trial requirements, safety labeling changes, and risk evaluation and mitigation strategies (REMS).

FDAAA gave FDA new authority to require post-marketing clinical trial and epidemiological studies, safety-related labeling changes, and REMS, under certain circumstances. FDAAA specifies in the new REMS authority provisions that certain determinations concerning REMS are to be made "in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug…" Under current delegations of authority, OND is responsible for reviewing and taking regulatory actions concerning new drug applications (NDAs), biologic license applications (BLAs), and supplements to these applications, both pre- and post-approval. However, FDA interprets these FDAAA provisions as reflecting Congressional intent that OSE should be involved in making certain decisions regarding REMS, and this agreement reflects that intent.

II. MANAGEMENT OF SIGNIFICANT SAFETY ISSUES

Under this agreement, OND and OSE have equal responsibility for the resolution of significant safety issues affecting drug products and determining appropriate regulatory action. This agreement documents the Center's policy that, regardless of where the regulatory signatory authority officially resides, significant safety issues will be managed by interdisciplinary teams that include representatives from OND and OSE and other programs as needed, in accordance with mutually established workplans and timeframes.

Once a significant safety issue is identified, OND and OSE, with other programs as needed, will jointly determine the steps needed to resolve the issue and the appropriate regulatory action. Such steps and actions may include:

- requiring the sponsor to make safety labeling changes on the basis of new information (FDAAA, section 901, 121 Stat. 924, creating new section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA));
- requiring a sponsor to submit and implement a REMS (FDAAA, section 901, 121 Stat. 926, creating new section 505-1 of the FDCA);
- requiring a sponsor to conduct a post-market study or clinical trial (FDAAA, section 901, 121 Stat. 923, creating new section 505(o)(3) of the

FDCA)

- requesting an applicant to discontinue marketing;
- other actions such as working with sponsors to implement education plans for patients, or to modify promotion and advertising

III. STATEMENT OF INTENT

Recognizing the expertise of OSE in observational epidemiologic studies, proprietary name review, and medication error prevention, this agreement explicitly designates OSE as the lead office for certain regulatory actions in these areas, and also recognizes the expectation that, in the future, OSE will further expand its role in its other areas of expertise, such as pharmacovigilance activities, pharmaceutical risk management plans, and the review of carton and container labeling and packaging. Although the delegated authority for taking certain regulatory actions associated with approved applications (e.g., product approval, withdrawal of an application or approval of an additional indication) remains with OND or OPS at this time, the responsibility for signing certain letters to industry and the authority to approve some supplements will eventually be transferred to OSE. OSE is expected to further expand its role as it builds organizational capacity and has the personnel, expertise and resources needed to assume additional regulatory responsibilities.

IV. OSE DESIGNATED AS LEAD FOR CERTAIN REGULATORY ACTIONS

Under this agreement, OSE staff will play an expanded role in the resolution of significant drug-related safety issues and assume lead regulatory responsibility for areas related to observational epidemiologic studies and medication error prevention as described below.

OSE, with input from OND and OPS, will develop a plan with a phased approach to implementing the transfer of scientific lead functions and assumption of signatory authority for regulatory actions related to these activities. Changes to the delegations of authority will be proposed to implement these changes at the appropriate time.

A. Observational Epidemiologic Studies

When a safety issue arises, a population-based observational epidemiologic study may be needed to better characterize the safety issue and quantify the risk so that FDA can determine the appropriate regulatory action. If OND and OSE decide that an observational epidemiologic study is needed, OSE will coordinate reviews related to the study, assemble review teams that include other programs as needed, and take the lead on working to achieve consensus on whether such a study will be conducted by FDA, another party, or required under FDAAA (regulatory action). OSE will take the lead for communicating with industry regarding these studies.

Once it is determined that an observational epidemiologic study should be conducted by the sponsor, by FDA, or by others with FDA input:

- OSE will have the lead responsibility for reviewing protocols and evaluating study design proposals, and proposing modifications when appropriate.
- OSE will have the lead responsibility for reviewing completed epidemiological studies performed by FDA, sponsors, or outside groups that may support regulatory actions, and interpreting the results.
- OSE in collaboration with the Office of Biostatistics will be responsible for re-analyzing observational epidemiologic data sets as needed.

OSE will take the lead on working to achieve consensus on regulatory decisions related to these studies. In cases where a regulatory action is taken, OND or OPS will include recommendations and decisions from OSE in action letters, unless there is a disagreement over the recommendation in which case it will be promptly raised to the Director CDER as described in section V.

B. Medication Error Prevention

Proprietary Name Review

OSE will assume the lead in the review of proposed proprietary names or changes to proprietary names submitted by sponsors during the IND phase, or as part of an NDA, ANDA, BLA, or supplement. OSE will convene and lead a review team and will take the lead on working to achieve consensus on regulatory actions.

PDUFA IV goals include notifying application holders about the acceptance or non-acceptance of proposed proprietary names submitted to INDs or with NDAs/BLAs within specified timeframes. OSE will have the lead responsibility for communications to industry regarding proprietary name review, including letters (e.g., information request letters and letters with the tentative acceptance or non-acceptance decisions prior to final action on applications), teleconferences, and meetings, with the following exceptions. In cases where notification of acceptance or non-acceptance decisions on a proposed proprietary name is performed in conjunction with other regulatory actions for which delegation of authority is not with OSE, OND or OPS will include recommendations and decisions from OSE in action letters, unless there is a disagreement over the recommendation in which case it will be promptly raised to the Director CDER as described in section V.

Review of protocols and studies that assess medication error risk

OSE will assume the lead in the review of protocols and studies that assess medication error risk performed by FDA, sponsors, or outside groups that may support regulatory actions. OSE will convene and lead a review team and will take the lead on working to achieve consensus on regulatory actions. In cases

where regulatory action is taken in conjunction with other regulatory actions for which delegation of authority is not with OSE, OND or OPS will include recommendations and decisions from OSE in action letters, unless there is a disagreement over the recommendation in which case it will be promptly raised to the Director CDER as described in section V.

V. ACCOUNTABILITY

As the Directors of OND and OSE, we acknowledge that we will be held accountable and are expected to hold our staff accountable for acting in accordance with the provisions of this agreement. We commit to ensuring that:

- Significant safety issues are tracked and resolved in a timely manner
- Interdisciplinary teams are formed to address significant safety issues, and every member of the team is provided an opportunity to express his or her view on the appropriate resolution of the issue.
- In many (or even most) cases, it is anticipated that the review team will reach agreement on the appropriate regulatory action; however, if there are differences of opinion about the appropriate action that cannot be resolved between the Directors of the offices involved, then the disagreement will be promptly raised to the Director, CDER, for resolution, with a full and adequate record documenting the different views expressed on the issue and the options for resolution.

VI. ADMINISTRATIVE PROCESS

OND and OSE agree to promptly establish the necessary procedures to ensure adequate communication and a consistent approach to the interpretation and application of this agreement.

The agreement is entirely procedural in nature, does not formally bind FDA, and creates no new rights or obligations for FDA or any regulated entities. The document reflects CDER's current position on the appropriate assignment of organizational roles and responsibilities that continues to evolve.

For further information contact:
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VII. EFFECTIVE DATE AND REVIEW/RENEWAL

This agreement takes effect on June 16, 2008. Within one year of the effective date, CDER will evaluate this agreement and make appropriate modifications. To ensure that this review occurs within one year, this agreement will lapse pending renewal on June 16, 2009.

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John Jenkins, M.D.
Director, OND, CDER

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Gerald Dal Pan, M.D., M.H.S.
Director, OSE, CDER

Concurrence:

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Janet Woodcock, M.D.
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