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 renews 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 drug applications 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 pharmacoepidemiological 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.

CDER is working on documenting policies and procedures in MAPPs that will operationalize the principles contained herein, and thus ultimately render this MOA obsolete.

Reviews of applications and supplements have long relied upon a multidisciplinary team-based approach. OSE had 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, and in

keeping with CDER's equal voice principles as described in section V, significant safety issues will be managed by interdisciplinary teams that include both OND and OSE and other disciplines with relevant expertise. Furthermore, 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 lead responsibilities for certain other regulatory actions 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 studies and clinical trials, 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 CDER policy, OND is responsible for signing certain regulatory letters 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 pharmacoepidemiologic 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 under current CDER policy, the responsibility 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 has been transferred to OSE as described below, and the authority to sign other letters and 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 continue to play an expanded role in the resolution of significant drug-related safety issues and assume lead regulatory responsibility for areas related to observational pharmacoepidemiologic studies and medication error prevention as described below.

On April 29, 2009, certain signatory authorities were delegated to specified OSE officials, as described in section 1410.104 of the Staff Manual Guide (http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049625.html). OSE, with input from OND and OPS, has developed and implemented a plan to exercise its signatory authority related to the acceptability of proposed proprietary names, and will develop a plan with a phased approach to implementing the transfer of other scientific lead functions and assumption of signatory authority for regulatory actions related to these activities when it has the necessary personnel, expertise and resources.

A. Observational Pharmacoepidemiologic Studies

When a safety issue arises, OND and OSE, with other offices as needed, will jointly decide whether a population-based observational pharmacoepidemiologic study is needed to better characterize the safety issue and quantify the risk so that FDA can determine the appropriate regulatory action. OND will provide scientific and medical background on safety issues and will give input to the review team as to the adequacy of the study protocol and results to address the safety issue.

When OSE has the necessary personnel, expertise and resources, it will take on the lead responsibility for observational pharmacoepidemiologic studies. Once that transfer occurs, if OND and OSE, and other programs as appropriate, decide that an observational pharmacoepidemiologic 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 coordinate such reviews for all observational pharmacoepidemiologic studies that will be the basis for regulatory decision making (e.g., submitted to the application or included in advisory committee discussions), regardless of whether the study reports or protocols were required by FDA. In addition, OSE will take the lead for communicating with industry regarding these studies.

Once it is determined that an observational pharmacoepidemiologic 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.
- reviewing completed pharmacoepidemiological studies performed by FDA, sponsors, or outside groups that may support regulatory actions, and interpreting the results.
- in collaboration with the Office of Biostatistics, re-analyzing observational pharmacoepidemiologic data sets as needed.

Finally, 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 has taken 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 convenes and leads the review team and takes 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 has the lead responsibility and the signatory authority 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 the responsibility for taking regulatory action 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

When OSE has the necessary personnel, expertise and resources, 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 related to medication error risk is taken in conjunction with other regulatory actions for which OND or OPS have the responsibility, 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.
- Each office informs the other as soon as possible after a significant safety issue is identified so that appropriate staff can be present at all meetings of the interdisciplinary teams.
- Adequate background summaries and documents are made available to the entire team.
- Every member of the team is provided an opportunity to express his or her view on the appropriate resolution of the issue.

Since this MOA was first put into place, CDER has further developed the concept of "equal weight" described above, now called "equal voice." When a decision is to be made in CDER, all disciplines with relevant expertise should be represented in the decision-making process. The team is in alignment when, following a full discussion and understanding of the issue, all disciplines can support the decision to be made, even if one or more review disciplines is not in complete agreement with the decision. If there is not alignment between all relevant disciplines, the review team will escalate the decision by "widening the circle" to include increasingly higher levels of management within each discipline until alignment can be achieved. The escalation will continue up the management chain of each discipline until Office Directors and Super-Office Directors are involved. If alignment cannot be achieved at this level, the decision will be raised to the Center Director or his/her designee.

VI. ADMINISTRATIVE PROCESS

OND and OSE agree to continue establishing 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, 2009. 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, 2010.

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Concurrence:

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