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Kaiser Foundation Health Plan, Inc.
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December 22, 2009

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Citizen Petition under 21 C.F.R. §10.30

Dear Sir or Madam:

Enclosed please find the Citizen Petition submitted by Kaiser Permanente regarding the Risk Evaluation and Mitigation Strategies programs (Section 505-1 of the Food, Drug and Cosmetic Act).

Respectfully submitted,

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FDA-2009-P-0602

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Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
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Docket No. _____

CITIZEN PETITION

Petitioner Kaiser Permanente[1] hereby submits this citizen petition under 21 C.F.R. §10.30. Petitioner requests that the Food and Drug Administration ("FDA") take the actions described below.

I. ACTION REQUESTED

Kaiser Permanente requests that the FDA revise its standards, procedures and guidelines for the development, implementation, and evaluation of Risk Evaluation and Mitigation Strategies ("REMS") programs to comply fully with Section 505-1 of the Food, Drug and Cosmetic Act (the "FFDCA" or the "Act"). Specifically, Kaiser Permanente requests that the FDA:

1. Increase the transparency and opportunity for comment by health care providers and other members of the public in the development process for REMS that include elements to assure safe use ("ETASU").

[1] The Kaiser Permanente Medical Care Program, or "Kaiser Permanente," refers to several closely cooperating organizations that make up America's largest private integrated health care delivery system. It comprises Kaiser Foundation Health Plan, Inc., the nation's largest nonprofit health plan, the nonprofit Kaiser Foundation Hospitals, and the Permanente Medical Groups, seven independent physician group practices that contract with the Health Plan to meet the health needs of Kaiser Permanente's 8.7 million members in nine states and the District of Columbia.

2. Make summary data collected by REMS programs and findings from assessments of REMS programs publicly available so that health care providers and patients have the opportunity to review the information objectively and use it in making health care decisions.
3. Regularly evaluate the ETASU required as part of a REMS program to assess their effectiveness and include health care providers in the evaluation process.
4. Ensure that drug companies do not use requirements in REMS programs to give preferential treatment to certain health care providers.
5. Guard the confidentiality of protected health information ("PHI") by ensuring (a) that collection of PHI is required only when essential to an effective REMS, using a minimum necessary standard; (b) that PHI and provider information disclosed for a REMS shall only be used to satisfy the REMS requirements; (c) that no patients or providers are requested to authorize disclosure of PHI for any purpose beyond the immediate requirements of the REMS; and (d) that the identity of all entities to whom PHI and provider information has been disclosed and the reasons for each disclosure are known.

II. STATEMENT OF GROUNDS

A. Introduction

Kaiser Permanente, America's largest private integrated health care delivery system, is involved in virtually all aspects of health care delivery, providing not only health insurance coverage but also medical care through physicians, clinics, hospitals, pharmacies (including specialty pharmacy services) and laboratory services. Thus, the

requirements associated with REMS programs have a significant impact on Kaiser Permanente. In addition, Kaiser Permanente's experience across the spectrum of health care delivery gives it a unique perspective on how REMS programs impact various aspects of the delivery system.

The statutory REMS provision, Section 505-1 of the Act, requires the FDA to obtain "input from patients, physicians, pharmacists and other health care providers about how the elements to assure safe use . . . for 1 or more drugs may be standardized so as not to be . . . unduly burdensome on patient access to the drug" and "to the extent practicable, minimize burden on the health care delivery system." It also requires yearly evaluation of the ETASU requirements for one or more drugs. To our knowledge, neither of these statutory requirements has been met. Further, although the FDA has implemented the statutory provisions by imposing REMS requirements on numerous drugs, it has not publicly sought input from patients, physicians, pharmacists, or other health care providers regarding the development of REMS for any new drugs and only for one class of already-approved drugs (*i.e.*, the REMS currently under consideration for opioids). Moreover, to our knowledge, no evaluations have been conducted.

As a result, the FDA is imposing REMS developed without due consideration to existing health care delivery systems. Some REMS requirements, in particular ETASU, are unduly burdensome on health care systems and could adversely impact appropriate patient access to drugs. Most REMS with ETASU through late 2009 have involved drugs with relatively small target populations. Applying ETASU to drugs that have larger target populations, such as opioids or erythropoietin stimulating agents ("ESA"), will have a much greater impact on health care delivery systems. As set forth below, Kaiser

Permanente urges the FDA to implement the REMS provisions in a manner consistent with the statute, soliciting health care provider expertise to avoid ETASU designs that overburden existing health care systems.

Kaiser Permanente also urges the FDA to periodically review REMS programs to determine whether the benefits outweigh the significant costs. REMS with ETASU can substantially increase the workload burden and costs associated with the prescribing, dispensing, administration and management of certain drugs, many that are already high-priced and resource intensive. Soliciting input and evaluating REMS programs after implementation would better ensure that REMS requirements appropriately preserve provider and patient access to the drugs and would take into account the characteristics of current delivery systems.

Kaiser Permanente also urges the FDA to make more summary data publicly available from safety findings from ETASU in REMS. Objective reviews – *e.g.*, from the FDA reviewers and not from the drug companies – could benefit FDA's safety goals and public health by providing better perspectives on safety risks; the identification, diagnosis, and treatment of adverse events; and how or whether risk mitigation strategies have improved patient safety. Making such information available to health care providers will generally allow them and their patients to make better informed medical decisions.

The FDA also should ensure that drug companies do not use certification requirements in REMS programs to unfairly limit some health care providers' ability to prescribe, dispense or administer drugs subject to REMS while facilitating this ability for selected providers who have contracted with the drug company.

Finally, patient and health care provider privacy is an important issue that has not been addressed by the FDA in its approval, evaluation, or implementation of REMS programs. Kaiser Permanente urges the FDA to ensure that drug companies are not using data or information collected as part of a REMS program for reasons unrelated to the public health concerns that triggered the REMS requirement.

B. Background

1. Kaiser Permanente

Kaiser Permanente is America's largest private integrated health care delivery system. It comprises Kaiser Foundation Health Plan, Inc., the nation's largest nonprofit health plan; the nonprofit Kaiser Foundation Hospitals; and the Permanente Medical Groups, seven independent physician group practices that contract with the Health Plan to meet the health needs of Kaiser Permanente's 8.7 million members in nine states and the District of Columbia. Most pharmacy, diagnostic, and laboratory services are performed within the Kaiser Permanente system. As part of its commitment to high quality care, Kaiser Permanente has made a significant investment in developing its secure Electronic Health Record ("EHR") system, KP HealthConnect®, to support the delivery of care to its members and to enhance communications among the medical professionals who serve them.

Kaiser Permanente has a well-established electronic prescribing system, which is fully integrated with KP HealthConnect and Kaiser Permanente's owned and operated pharmacy information management system ("PIMS"). This system allows a physician to immediately view a patient's laboratory or radiology results, consultant physician

findings (*e.g.*, from a specialist also evaluating the same patient), pharmacy records showing whether and when prescriptions are being filled, and other information that is critical to coordinated care. In addition to a patient-centric view of drug therapy, Kaiser Permanente's information systems and integrated structure also support an aggregated examination of drug therapy program-wide, including formal, centralized processes to assess available evidence about new and approved drugs. The combined experience of Kaiser Permanente providers can be amassed to develop clinical guidelines or other decision support tools. The EHR system allows a review and analysis of usage patterns, safety concerns and other clinically valuable information. Kaiser Permanente has also created an internal specialty pharmacy program and a dispensing specialty pharmacy, which handles drugs with intensive REMS requirements such as ETASU.

2. Section 505-1 of the Federal Food, Drug and Cosmetic Act

The Food and Drug Administration Amendments Act of 2007 ("FDAAA") includes section 505-1 of the FFDCA, which gives the FDA the authority to require a REMS if it determines that such a strategy "is necessary to ensure that the benefits of the drug outweigh the risks of the drug."[2] The FDA also may require a REMS for a previously approved drug if the FDA "becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug."[3]

Pursuant to section 505-1(d), all REMS must have a timetable for submission of assessments of the REMS. In addition, REMS may include any or all of the other elements listed below if specified criteria are met:

[2] Section 21 USC § 331;505-1(a)(1).
[3] Section 505-1(a)(2)(A).

- A Medication Guide (section 505-1(e)(2)(A))
- A patient package insert (section 505-1(e)(2)(B))
- A communication plan to health care providers (section 505-1 (e)(3))
- Elements to assure safe use ("ETASU") (section 505-1(f)), which may also include an implementation system.

ETASU may be required if a drug, which has been shown to be effective but is associated with one or more serious adverse event(s), can be approved only if such elements are part of a strategy to mitigate a specific risk. ETASU may include certain restricted distributions, procurement, and dispensing systems. For example, only health care providers with certain training or experience may be permitted to prescribe or dispense a drug, or the drug may be dispensed only in certain health care settings, such as hospitals.

The ETASU may also require that the drug be dispensed to patients only with evidence or other documentation of safe use conditions, such as laboratory test results, or the ETASU may require that patients using the drug be subject to certain monitoring. In effect, this creates a separate category of drugs, which require considerably more labor in the health care delivery setting to satisfy REMS ETASU requirements and to provide the drug in the safest manner possible. By design, section 505-1(f) makes some drugs available that would otherwise not be dispensed outside of an investigational setting, expanding treatment options for patients.

In subsection (f), Congress directed the FDA to ensure that ETASU not be unduly burdensome on patient access and, in order to "minimize burden on the health care delivery system," to design ETASU that are compatible with established distribution, procurement and dispensing systems.[4] The statute directs the FDA to evaluate and

[4] Section 505-1(f)(2)(D)(ii).

assess, annually at a minimum, whether ETASU on one or more drugs meet these goals; to issue or modify Agency guidelines; or, if necessary, to modify ETASU to meet such goals.[5]

Subsection (f) also requires that the FDA "seek input from patients, physicians, pharmacists, and other health care providers about how ETASU under this subsection for 1 or more drugs may be standardized so as not to be . . . unduly burdensome on patient access to the drug" and "to the extent practicable, minimize the burden on the health care delivery system."[6]

3. The FDA's Implementation of REMS

Since the enactment of the FDAAA, the FDA has approved about 90 REMS for new drugs and has requested REMS for many other products.[7] In addition, pursuant to section 909(b)(1) of the FDAAA, sixteen products approved prior to enactment of the FDAAA with ETASU (typically as part of an approved RiskMAPs) have been deemed to have in effect an approved REMS.[8]

On September 30, 2009, the FDA issued a Draft Guidance for Industry, "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS

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[5] Section 505-1(f)(5)(B) and (C).
[6] Section 505-1(f)(5)(A).
[7] *See* *http://www.fda/gov/drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.*
[8] *See* 73 Fed. Reg. 16313 (March 27, 2008). Before the FDAAA was enacted, the FDA had approved a small number of drugs and biological products with risk minimization action plans (RiskMAPs). RiskMAPs were programs designed to minimize the known risks of a product while preserving its benefits, specifically through strategies that would go beyond safety reporting and labeling that described the product's risks and benefits. Although REMS will henceforth replace RiskMAPs, and products with RiskMAPs that include ETASU have been deemed to have REMS, there are still a few RiskMAPs remaining. We understand that ANDAs for those products will be approved with comparable RiskMAPs or REMS programs.

Assessments, and Proposed REMS Modifications."[9] The draft document offers guidance on the format and content of proposed REMS; the content of assessments and proposed modifications of approved REMS; the appropriate identifiers to use on REMS documents; and how to communicate with the FDA about REMS.

Although the FDA has required REMS programs for more than 100 new or existing drugs, to date it has solicited public input only in the case of a proposed REMS for opioids.[10] The REMS for all other products have been issued without seeking input from the public.

4. Impact of REMS on the Health Care Delivery System

Until recently, health care providers and patients learned about RiskMAP and REMS programs only from the drug companies implementing the programs. The FDA now posts a list of approved REMS on its website, making the content of newly-approved REMS available to health care providers and the public. Still, providers and patients continue to have little or no input into the development of these programs, which are intended to enhance safety for certain hazardous drugs. Yet, the impact on the health care delivery system has been substantial.

Within Kaiser Permanente's California operations, many pharmacy employees have been re-directed from other functions to assure compliance with the REMS for some drugs with ETASU requirements. For other REMS, depending on the requirements and the frequency of prescriptions, small incremental workload elements must be rolled into

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9 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

10 *See* 74 Fed. Reg. 17967 (April 20, 2009), Notice of Public Meeting; 74 Fed. Reg. 53509 (October 19, 2009), Extending the Comment Period until October 2010.

daily dispensing activities (such as any added workload for distribution of Medication Guides and the resulting provider-patient conversations).

Despite the added workload for REMS ETASU, it remains important for Kaiser Permanente to acquire such drugs and dispense them to members within the requirements of the REMS. Yet several manufacturers have attempted to justify the use of specific, contracted specialty pharmacies for distribution of their product citing REMS requirements or "agreements" with the FDA.[11] Many of these claims have been misstated. In those cases where a REMS ETASU actually does exist, the drug company has established the contracted relationship prior to public announcement of the REMS requirements. This means that the outside specialty pharmacy must be used until a Kaiser Permanente arrangement can be made.

One potentially serious consequence of removing dispensing, or medication management from Kaiser Permanente's delivery system is the impact on coordination of care. When these critical aspects of treatment occur outside of KP HealthConnect® and PIMS, crucial clinical data will not be captured in the patient's electronic medical record and treating providers will not have a comprehensive record for medical decision-making. Also, valuable evidence will be missing from other internal systems used to monitor drug usage, safety issues, and prescribing patterns. Kaiser Permanente has its own specialty pharmacy program and can accommodate ETASU; it should not be forced to outsource dispensing of the product.

[11] Kaiser Permanente and other consumers pay a premium for drugs acquired through these specialty pharmacies. The pharmacies charge prices that exceed wholesale acquisition cost ("WAC"), the list price for drugs that otherwise would be purchased through a drug wholesaler. Kaiser Permanente would ordinarily purchase these drugs through a wholesaler or directly from the drug company, often with a negotiated discount from WAC.

Finally, those REMS programs with ETASU often require that patients disclose PHI[12] and that prescribers register with information about their background and medical practice. It is not always clear that all of the information requested by the drug company is needed to administer a REMS program intended to enhance patient safety. Moreover, the required disclosures raise concerns that the information obtained may be used for marketing or other purposes with no relation to the REMS program. For example, drug companies often require patients to sign broad authorizations before allowing the patient access to a drug. Authorizations for disclosure of PHI are generally not required under the Health Insurance Portability and Accountability Act ("HIPAA")[13] Privacy Rule for FDA safety monitoring activities; nevertheless, many such authorizations allow drug companies to share the patient's information with third parties for any purpose.

C. Discussion

1. The FDA should increase transparency and opportunity for public comment in the development, implementation, and assessment of REMS programs.

In the last year, the FDA has taken some important steps to improve public access to information about REMS programs and to make specific REMS requirements more transparent to health care providers. For example, the FDA has begun posting newly approved REMS on its website. We recommend that the FDA extend this open, transparent approach to the development of REMS for new drugs during the approval process rather than waiting until after the FDA approval to reveal details of the REMS. This more transparent approach would be especially important for REMS containing

[12] As defined under the Health Insurance Portability and Accountability Act ("HIPAA").
[13] 45 CFR Parts 160 and 164 (Subparts A & E).

ETASU, which are the most restrictive forms of REMS and the most difficult for health care systems to implement.

We propose that the FDA regularly provide the public an opportunity to comment on all REMS that require ETASU being considered for new and previously approved drugs. The FDA has already taken this significant step with the proposed class REMS for opioids. The opportunity for public comment should be formalized into a process that assures considered perspectives from health care providers who will be involved in the application of the ETASU.

Section 505-1(f)(2)(D) of the Act requires that each ETASU shall, to the extent practicable, conform with ETASU for other drugs with similar risks and be designed to be compatible with established distribution, procurement and dispensing systems for drugs so as to minimize burden on the health care delivery system. Section 505-1(f)(5) requires the FDA, through the Drug Safety and Risk Management Advisory Committee, to seek input from health care providers about how ETASU can be standardized so as not to be unduly burdensome on patient access and to the extent practicable to minimize burden on the health care delivery system.

These statutory provisions clearly seek an approach to REMS with ETASU that are consistent with current practices and procedures and not overly burdensome to the health care delivery system. Despite these statutory directives, the FDA has taken few steps to ensure drug companies have considered these care delivery system factors in developing REMS for their drugs. As previously described, REMS with ETASU essentially create a whole new class of drugs from the delivery system and cost perspectives. Nevertheless, the development of REMS has been one-sided, excluding

key constituents able to represent the delivery system issues. The functional, day-to-day impact of REMS with ETASU is much greater on health care systems and patients than it is on the drug company sponsor. Thus, as a matter of fairness and in the public interest of minimizing impacts on the delivery system, all parties involved in an ETASU implementation should be part of the REMS design process or at least have a voice prior to final FDA approval of REMS.

In the context of new drug approvals, the transparency of the Advisory Committee process lends greater credibility to the FDA's drug approval process, and gives health care providers the opportunity to assess information about the efficacy and safety of a new drug under review. Using the Advisory Committee approach or another mechanism that fosters open discussion about safety and efficacy could improve REMS ETASU design, eliminate or mitigate unforeseen problems with the REMS, assure better compatibility between an ETASU and existing health care systems, and improve the credibility of the REMS design process.[14]

Thus, Kaiser Permanente urges the FDA to regularly convene an Advisory Committee that would be responsible for making recommendations regarding the ETASU elements in a proposed REMS program. The Advisory Committee should include members who are health care providers because they are aware of the impact ETASU would have on health care delivery. They are also in the best position to know whether a particular ETASU conforms to ETASU for other drugs with similar risks and whether the proposed ETASU design will be compatible with established distribution, procurement and dispensing systems for drugs so as to minimize burden on the health care delivery

[14] Under section 505-1(h)(6), the FDA may convene meetings of advisory committees to review safety concerns prior to REMS assessment as well as to evaluate REMS for particular drugs or classes of drugs.

system. An Advisory Committee dedicated to ETASU review will have the substantive expertise and also the historical knowledge needed to develop effective and targeted ETASU that advance the safety of drugs while minimizing the cost of ETASU on the health care system.

Kaiser Permanente understands that it may take some time for the agency to institute new advisory committee procedures for REMS with ETASU. As an interim measure, Kaiser Permanente urges the FDA to take advantage of the processes that are in place in the context of drug approvals. Thus, if the FDA is planning to require REMS with ETASU for a drug already scheduled for review by an Advisory Committee, that Advisory Committee process should simultaneously be used to solicit public input and advice on the ETASU, as well as input on issues pertaining to whether the drug should be approved.

The FDA should include one or more advisory committee members who are health care providers for the discussion and recommendations pertaining to the ETASU. For drugs that are not scheduled for review by the Advisory Committee, the FDA should develop a temporary, alternate public process to solicit input at the same time that the drug could have gone before an Advisory Committee. The FDA could also use this alternate public process in cases where discussion of the ETASU at the scheduled Advisory Committee is not feasible.

Kaiser Permanente urges the FDA to adopt an Advisory Committee (or similar) approach not only to comply with the particular requirements in the statute,[15] but also because input from different health care providers would help ensure REMS programs are more workable and more effective. When the parties responsible for making a

[15] Section 505-1(h)(6).

program work on an operational level are involved in the early development, ETASU will align more closely with established distribution, procurement, and dispensing systems, as the statute envisions.

Because of its integrated health care delivery system, Kaiser Permanente is well situated to evaluate the clinical and practical impact of REMS across many parts of the health care system, and provide valuable feedback about different aspects of a REMS program. Yet to date, Kaiser Permanente and other health care providers have not had the opportunity to evaluate and possibly improve on either proposed or existing REMS designs.

There are several examples that demonstrate how input could have improved the development of a risk management plan. One such example is the isotretinoin safety program, designed to reduce fetal exposure to the drug. The first system, launched in 2002, required physicians to place a yellow sticker on each prescription, a measure which did not accommodate electronic prescribing systems. Kaiser Permanente adopted an alternative approach that was shown to be as effective, but more efficient for the Kaiser Permanente system.[16] Had Kaiser Permanente been at the table when the program was developed, flexibility to accommodate electronic prescribing could have been permitted up front. It is important that REMS programs with ETASU have such flexibility, because there may be various ways to accomplish REMS goals and some approaches may lessen the burden on the health care system without reducing the overall program effectiveness.

[16] Cheetham TC, Wagner RA, Chiu G, Day JM, Yoshinaga MA, Wong L. A risk management program aimed at preventing fetal exposure to isotretinoin: retrospective cohort study. *J Am Acad Dermatol.* 2006 Sep;55(3):442-448.

The subsequent iPLEDGE program,[17] launched in 2005, was equally flawed in not allowing such flexibility. Initially, patients other than women of child-bearing potential were required to participate, alternative dosing for oncology use was not accommodated, patients were locked out of access based on a 7-day window, and lengthy online patient training was required. These complications had to be addressed after implementation due to lack of foresight in planning iPLEDGE. The use of isotretinoin dropped significantly, suggesting that the safety program may have affected therapeutic choice beyond the intent of the program. Reducing pregnancies in the patient population receiving the drug can be accomplished in various ways; the program will be most effective when the different prescribing systems are taken into account.

An open dialogue among various providers may have predicted and thus reduced some implementation problems. In general, a policy of seeking and using input will help to identify different solutions, create appropriate flexibility, and proactively address problems – all of which will decrease the likelihood that proposed REMS would interfere with appropriate patient access and the delivery of care

The cost of health care is a high-level national concern. Input from health care providers could help to ensure that costs imposed by REMS ETASU are justified, possibly even minimized, because providers can demonstrate how to capitalize on existing systems or how to develop new processes that build on current systems.

[17] U.S. Food and Drug Administration. "iPLEDGE Information." Last updated April 30, 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094307.htm. Accessed November 29, 2009.

2. The FDA should make data collected as part of REMS programs publicly available so that health care providers and patients have access to such information and can use it to make better health care decisions.

Under the statutory mandate for REMS assessment, drug companies must submit REMS data to the FDA, so it can evaluate whether a particular REMS is effective. Many ETASU include patient registries, diagnostic and usage data, questionnaires, adverse events reports, and other data submissions. Both consumers and health care providers have a substantial interest in learning about issues related to a drug's safe use; thus, these data also should be publicly available in summary form. The FDA should make data obtained through REMS ETASU available in de-identified form for objective analysis. Such a rich data resource would allow parties other than the manufacturer to identify potential safety issues and to gauge the effectiveness of risk mitigation strategies.

A case in point is the use of natalizumab (Tysabri®) to treat patients with multiple sclerosis or Crohn's disease. The REMS (then a RiskMAP) began in 2006. In September 2009, the FDA posted limited updated information concerning 13 reported cases of progressive multifocal leukoencephalopathy ("PML") diagnosed in patients treated with Tysabri in the U.S. and Europe with additional information about the duration of Tysabri treatment before PML was detected. By October 2009, other sources announced an increase to 23 cases of PML and some lessons from these reports of PML were incorporated into revised package labeling for Tysabri. However, very little information has been available regarding how PML cases were identified and diagnosed, how patients with PML were treated, and what outcomes are known for those patients. This information – in case reports and conglomerated data – could better prepare prescribers for dealing with the adverse event of PML and should be provided by an

unbiased source such as the FDA. Of course, any data disclosure should be consistent with applicable law governing the privacy and security of individually identifiable information.

Posting briefing documents from FDA Advisory Committee meetings – a practice begun earlier in this decade – represents a major advance in open sharing of critical clinical trial evidence with health care providers and systems across the country. The Advisory Committee process provides data and information that might not otherwise be available to the public, lends greater credibility to the FDA drug approval process, and gives health care providers the opportunity to assess information about efficacy and safety of a new drug under review.

As an example, briefing documents from the 2003 pre-approval Advisory Committee meeting about omalizumab (Xolair®) reviewed crucial safety information, including the question of whether the drug might contribute to malignancy risk and the possible mechanisms by which malignancies might occur. This safety information enabled healthcare organizations to balance potential risks versus benefits and helped to clarify that exposure to this newer drug should be an alternative only after other existing treatments had been tried.

Subsequently, the FDA has identified and publicized other safety signals for Xolair. Such information – from Advisory Committee documents or from later disclosures – may be far more valuable than a patient registry or other ETASU in assuring that a drug is used in the context of its attendant risks and benefits.

Health care providers and patients are being asked to submit considerable amounts of data to REMS ETASU programs. Some useful information should come

back from those programs, and we recommend that the FDA establish a mechanism for providing this information. First, the health care providers caring for patients taking these drugs should have this information to better understand and monitor treatment. In addition, some potential conflicts of interest would be mitigated. Drug company sponsors would not be the sole source of information regarding adverse events that could negatively affect perceptions of their product. While drug company sponsors may vigorously oppose releasing such information because of the possible impact on commercial viability, we believe the issues of patient safety and health care provider knowledge strongly outweigh commercial concerns.

3. The FDA should regularly evaluate the ETASU to assess the effectiveness of the REMS program.

Section 505-1(f)(5)(B) directs the FDA to, at least annually, evaluate one or more drugs to assess its ETASU and after considering such input, if necessary to modify its guidance or implementation of the ETASU. Although the REMS provision is relatively new, there are a number of drugs for which REMS with ETASU have been in effect for well over a year. For those long-standing programs, the evaluation process to determine effectiveness should begin as soon as possible. The process should be extended to all drugs with ETASU with evaluation of data collected required at a reasonable milestone (*e.g.*, one year after data collection begins).

Evaluation of effectiveness is essential to the statutory purpose of REMS and ETASU.[18] When significant requirements are imposed on patients and health care

[18] *See* J. Woodcock, MD, "A Difficult Balance – Pain Management, Drug Safety, and the FDA," New England J Med 361;22 (Nov. 26, 2009) ("The FDA has been implementing strategies to reduce preventable harm from suboptimal use, misuse, and abuse of analgesics. Although these strategies are intended to ensure that risks are better managed, their effectiveness in reducing harm will require ongoing evaluation. For products that [require] REMS, metrics and procedures for tracking outcomes and the effectiveness of

providers through ETASU, it is vital to use the evidence obtained to demonstrate that the purpose of the REMS is being achieved. As described in subsection 505-1(f)(5)(B), evaluation should assess whether the ETASU actually does "assure safe use of the drug," whether ETASU "are not unduly burdensome on patient access to the drug," and whether ETASU, "to the extent practicable, minimize the burden on the health care delivery system."

REMS in general and ETASU in particular can be very costly to health care providers. Although Kaiser Permanente strongly supports appropriate use of the REMS programs to ensure drug safety, Kaiser Permanente urges the FDA to review these programs to determine whether there are actual benefits that justify the investments necessary to implement and administers REMS and whether those benefits offset the burdens on both patients and health care delivery. For this reason, Kaiser Permanente recommends the FDA develop strategies for meeting the statutory mandate to periodically evaluate existing REMS and to seek input from the public in general, and health care providers specifically.

Finally, seeking input and evaluating existing ETASU may ensure that future REMS programs primarily benefit patients and not drug companies, who may see REMS as means to further their own interests.[19]

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the interventions must be identified. The FDAAA requires each REMS to contain a timetable for its assessment that is unique to that drug. If risks are not adequately mitigated, then additional steps can be taken.")

[19] *See, e.g.*, "FDA's REMS Program – How It Can Hurt – or HELP – your Drug," http://www.windhover.com/ezine/html/REMSlp.html ("[T]here are numerous unlooked-for benefits to REMS. Sponsors who have already mastered the difficult process seem to have a smoother road the next time around. Then there are strict postmarketing requirements that often include practices, such as DTC marketing, that FDA has previously frowned on, so REMS could actually lend these activities new legitimacy and the stamp of FDA's approval." (emphasis added.))

4. The FDA should ensure that drug companies are not using ETASU requirements in REMS programs to selectively limit access for some health care providers to prescribe, dispense, or administer drugs subject to REMS, while facilitating access for contracted provider partners.

Pursuant to the ETASU provisions of the statute, the FDA may require (a) prescriber registries – specifying that certain drugs be prescribed only by health care practitioners with specific training or experience, who have obtained a certification – and/or (b) provider restrictions – specifying that a drug be dispensed only by pharmacies with certain certifications or in certain health care settings – and/or (c) patient registries. In some circumstances, such requirements can have the effect of preventing or limiting health care systems, such as Kaiser Permanente, from using their own high quality resources, providers, and facilities to dispense REMS drugs, educate providers and patients, and manage patient care.

For example, some drug companies have refused to certify Kaiser Permanente's pharmacies. Some companies have claimed that only their contracted partner specialty pharmacies are permitted or qualified to dispense the drug.[20] Restricting access without sufficient justification (*e.g.*, risk to patient safety from an alternative) is inconsistent with the requirement to "be compatible with established distribution, procurement and

[20] To date, the most objectionable attempts to limit access to a new drug have come from companies whose new drugs do not have a REMS ETASU, but who nevertheless verbally assert that the FDA requires a patient registry. When pressed for documentation, some companies have backed away from those claims, but sometimes only after months of restricted access. Those companies may be motivated by a desire to collect as much patient and prescriber data as they can for their own purposes. A drug company sponsor who wants complete records of prescribers or patients for a rare disease (treated with their drug at very high cost per patient) might find ways to use information from a patient registry for promotional purposes. We also understand that in at least one case, a brand has used the REMS requirement to prevent a potential ANDA applicant from obtaining the drug product sample needed to conduct testing required by the FDA as part of the ANDA application. (*See e.g.*, Docket No. 2009-P-0266).

dispensing systems for drugs so as to minimize burden on the health care delivery system."[21]

While Kaiser Permanente does not object to physician or pharmacy certification requirements *per se*, Kaiser Permanente strenuously objects to drug companies unreasonably dictating who can prescribe, dispense, or administer their products. If health care providers, pharmacies, or health care facilities can meet the certification requirements of the REMS, the drug company should not be able to prevent them from prescribing, dispensing or administering the drug. Nothing in statute requires the FDA to permit drug companies to assume this level of control, which is plainly anti-competitive.[22] Kaiser Permanente urges the FDA to take appropriate steps to ensure that drug companies are not allowed to unreasonably deny the right to prescribe, dispense or administer their drugs.

Since the FDA has started posting concise REMS documents on its website, incidents of misrepresentation of REMS requirements, specifically ETASU, have declined and we believe the posting will deter future attempts. We recommend the FDA openly oppose inappropriate or unnecessary access restrictions by drug companies with a REMS ETASU and that the FDA take steps to ensure that drug companies without FDA-mandated REMS programs are not restricting access to their drugs.

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[21] Section 505-1 (f)(5).

[22] As noted in footnote 11, *supra*, controls over the distribution channel for certain REMS drugs has inflated the costs of those drugs by eliminating the ability of purchasers to negotiate on drug prices.

5. The FDA should assure that REMS are implemented in a manner that ensures the privacy of patient protected health information

As a general matter, the HIPAA Privacy Rule requires signed authorization before a covered entity, such as a provider or a health plan, can use or disclose an individual's PHI. Under certain circumstances, however, covered entities are permitted to disclose an individual's PHI to persons (or organizations, such as drug companies) subject to FDA jurisdiction for public health purposes related to the quality, safety or effectiveness of an FDA-regulated product without first obtaining such authorization.[23]

Disclosures of PHI under the public health exception must be limited to the minimum amount necessary to accomplish the public health purpose. The disclosures that are made pursuant to a signed authorization, however, are not so limited.[24]

The permitted disclosure for public health purposes would cover disclosures of PHI related to a REMS program so long as 1) the disclosure of PHI is necessary to accomplish the safety objectives of the REMS and the amount of PHI disclosed is the minimum necessary to achieve that purpose; 2) the determination of minimum necessary is made by the covered entity disclosing the PHI under the REMS program; 3) the PHI is disclosed directly to the FDA-regulated person or entity, not to a third party; 4) the PHI is not used for any non-public health purpose; and 5) there is no further disclosure of the PHI.[25]

Even though the public health exception would permit disclosure of PHI in the context of REMS without an authorization, REMS patient enrollment forms typically

[23] 45 CFR § 164.512(b)(iii)
[24] 45 CFR § 164.502(b).
[25] 45 CFR. § 164.512. State law may impose additional restrictions on the use and disclosure of individually identifiable information by drug companies.

include authorization for disclosures to third parties for non-specified purposes. In fact, some REMS PHI disclosure authorizations expressly inform patients they will not be eligible to receive drug unless they sign the authorization.

Kaiser Permanente strongly objects to conditioning access to therapy on a disclosure of PHI. Patients or providers should not be required to authorize disclosure of PHI for any purpose beyond the immediate requirements of the REMS, in particular if that disclosure is required to obtain drug therapy. Kaiser Permanente questions the need for such authorization, given the permitted disclosures for a public health purpose, specifically those for the FDA-regulated entities engaged in safety activities. Kaiser Permanente also questions the overbroad and vague authorizations being sought. Using authorizations allow drug manufacturers to request and receive information beyond what a covered entity might deem the minimum necessary. Moreover, an authorization can explicitly permit further uses and disclosures beyond those related to the safety purposes of a REMS program. A drug company might find ways to use information from a patient registry for promotional purposes.[26]

Kaiser Permanente urges the FDA to amend its regulations or take other appropriate steps to ensure that drug companies are seeking only the minimum necessary information as permitted under HIPAA's public health exception and are not using the information collected pursuant to broad authorization under REMS for commercial or other non-public health purposes. One way to achieve this would be to require drug companies that seek collection of PHI or health care provider information through REMS

[26] Kaiser is also aware of at least on situation in which a drug company was using data collected as part of a REMS to meet its Phase IV study requirements. Kaiser also objects to research that uses such PHI information unless it complies with all applicable requirements governing research, including requirements regarding human subject protection,

programs, to, as a part of REMS assessments, identify all entities to whom PHI and provider information has been disclosed and to clearly state the reasons for each disclosure.

III. CONCLUSION

REMS programs, particularly those that include ETASU, impose significant burdens on the health care industry. While Kaiser Permanente supports programs to improve drug safety, it urges the FDA to take steps to ensure that the requirements imposed under REMS with ETASU are commensurate with the drug safety risks and are designed in a way that creates the least possible burden and thus has the least negative impact on patient access.

One important way to ensure this is to include those segments of the health care system that are required to implement the ETASU in the process of developing those requirements. As discussed above, such participation would go a long way towards ensuring that the REMS programs can be implemented effectively. Equally important is a commitment by the FDA to annually review ETASU requirements to ensure that they are accomplishing the goals for which they were developed. Again, participation by the health care industry is critical to effective evaluation.

One of the benefits of the ETASU is to collect information that the FDA and the drug company can examine to identify issues related to the safety of the drug. Kaiser Permanente urges the FDA to make summaries of that same information available to the public to create the opportunity for additional objective analysis of the information.

The FDA also should take steps to ensure that drug companies are not using REMS programs and ETASU requirements to unfairly advantage themselves or certain

health care providers while disadvantaging others. Specifically, the FDA should ensure that drug companies are not using ETASU requirements to unreasonably limit who can prescribe, dispense or distribute their drugs. The FDA also should ensure that drug companies are not inappropriately obtaining PHI and using it or other information they obtain through a REMS for their own commercial purposes.

The statutory REMS requirement provides valuable tools to improve drug safety. Kaiser Permanente urges the FDA to take steps to ensure that REMS are implemented in a way that helps patients without adding unnecessary, costly workload to the healthcare system and possibly impacting patient access to live-saving drugs.

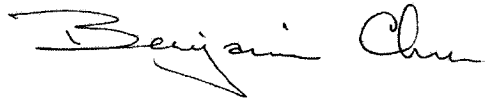
IV. ENVIRONMENTAL IMPACT

The action requested in this petition will have no impact on the environment.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition. A certification pursuant to section 505(q)(1)(H) of the FD&C Act is not required for this petition because it does not affect a pending application filed pursuant to section 505(j) or section 505(b)(2).

Respectfully submitted,



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