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Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
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[Submitted electronically to: www.regulations.gov]

RE: Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs;  
Notice of Public Meeting. [Docket No. FDA-2009-N-0143]

Dear Sir/Madam:

Thank you for the opportunity to provide comments on Risk Evaluation and Mitigation Strategies (REMS) for certain opioid drugs, published in the Federal Register on April 20, 2009 (74 FR 17967), regarding the Food and Drug Administration’s (FDA) intention to require a single REMS for long-acting and extended release opioid drug products formulated with fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings and the uniformed services.

APhA recognizes that FDA does not regulate pharmacies or pharmacists but regulates manufacturers and will hold them responsible for developing any REMS that FDA requires. However, pharmacists and prescribers [physicians, physician assistants, nurse practitioners, certain pharmacists authorized to prescribe under certain conditions in their state based on collaborative practice agreement(s), and other health care providers authorized to prescribe prescription medications] must implement these programs in their practices. They are the affected health care providers on the front-line of practice responsible for implementing any REMS, including any future opioid REMS, that are developed by manufacturers and approved by FDA. The Association is eager to work collaboratively with FDA, manufacturers and other stakeholders to develop a successful REMS solution. Solutions must ensure patient access and be designed with achievable and measurable outcomes. REMS must be either workflow neutral or provide compensation to those professionals who must implement them. There is simply no room in the workflow of physicians and pharmacists for additional uncompensated services.
On May 27, 2009, APhA testified at FDA’s two-day public meeting on opioid REMS. Our written comments build upon that statement and address question listed in the Federal Register meeting notice. Specifically, our comments focus on the need for a standardized, system-based approach with standard components selectively employed based on the intensity of the required REMS. Participant educational requirements should include specifics on REMS logistics and processes; familiarity with standardized components used in REMS, understanding of defined outcomes to guide matrix development; and essential pilot testing of any REMS prior to nationwide implementation. Additionally, we are including information from a June 2009 survey that we sent to APhA members to gather feedback on “lessons learned” from existing risk management programs and on potential components of an opioid REMS programs. The questionnaire was sent to 3,907 pharmacists practicing in community, clinic, and managed care settings. A total of 275 responded, resulting in a statistically significant 7% response rate.

Overview
As mentioned at the public meeting, APhA supports FDA’s efforts to assure appropriate use of long-acting and extended release opioids. However, many current risk management programs have presented challenges to prescribers and pharmacists. We must work together and learn from the past so that any challenges with opioid REMS are addressed and resolved prior to implementation and so that intended outcomes are achieved.

Pharmacists are challenged by the growing number of FDA-mandated REMS. All of these disparate programs lack standard processes, platforms and components. We are also concerned with the lack of standardization in the development process that creates these new components and systems/platforms for each new REMS. For example, there is wide variation in risk management program components such as: communication tools and plans, assessment processes, and in elements used to assure safe use. Additionally, elements to assure safe use can vary widely due to requirements for: prescriber and pharmacist training/education/certification; registries/enrollment; restricted distribution systems; dispensing based on safe use conditions; monitoring processes; implementation processes and systems; and patient responsibilities. These varied systems lead to administrative, logistical and workflow challenges. APhA appreciates FDA’s acknowledgment of these challenges during the recent FDA pharmacy stakeholder meeting and the opioid REMS public meeting.

Based on APhA member feedback on existing REMS programs, the following issues were identified:

- Nearly one-third of respondents selected the following as their top challenges: prescriber and patient registration, verification/documentation of education of prescriber/pharmacist, and verification procedures by pharmacist to process a prescription.
- In addition, respondents said that they had challenges with: verifying that specific lab test/results had been performed by the prescriber; addressing increases in suspect abuse or diversion prescriptions; and the time required to make multiple phone calls to address REMS processing glitches.
- Nearly one-third said that resolving REMS issues has a negative impact on their practice.
- Nearly a quarter of respondents said that they spend several hours or more a week resolving REMS issues.
A majority said that at least sometimes prescription claims processing was delayed because a REMS component was not met; the average delay being nearly half of a day or more.

Related to the impact of an opioid REMS — three-quarters of responders said that 1-25% of weekly prescriptions require a REMS; three-quarters said that up to 25% of weekly prescriptions are for long-acting/extended-release opioids, while a similar percent said that up to 50% of weekly prescriptions are for all opioids.

While we recognize that each new drug product requiring a REMS will have different risks to address, REMS must be designed to ensure that workable and long-range goals are met. We believe FDA must require a common framework and set of requirements that make each program more alike than different. We encourage FDA to work with the pharmacy and prescriber communities and other stakeholders to design in advance general concepts and principles that FDA could then require of manufacturers developing a REMS as a way to improve efficiency and standardization. America’s pharmacists call for a long-term visionary solution that will stand the test of time and benefit, not burden, all stakeholders involved and ultimately lead to improvements in patient safety. An overwhelming majority of survey respondents said a standardized, system-based approach for REMS should be developed using existing pharmacy technology/infrastructure that could be applied to manage REMS programs.

If we design for the long-term with a standardized, system-based process, then the requirements for complying with REMS can be streamlined and seamlessly implemented into prescriber and pharmacist workflows. For example, documenting that a pharmacist understands a program and attests to his or her ability and commitment to meet the requirements could be a standard process for any REMS, not a unique and potentially time consuming process for each different REMS. APhA believes that designing and implementing a REMS for certain opioids gives us an opportunity to create a standardized, system-based set of solutions for all REMS that, depending on the REMS, may vary by components (or modules) and levels of intensity based on each product’s risks for which the REMS is designed to mitigate. See Question B3 for additional information on this concept.

**APhA’s Responses to FDA Questions Listed in the Federal Register**

APhA offers the following comments on questions listed in the Federal Register meeting notice (74 FR 17967); we have designated A) for *Elements of REMS* questions, and B) for *Systems* questions.

**A. Elements of REMS**

1) **What type of education should be provided to prescribers and how this certification should be administered (e.g. through state Medical Boards, DEA, other Federal or state systems, or privately, through a contractor established to administer the REMS)?**

AND

2) **What type of education should be provided to pharmacists and others who dispense/administer and how this certification should be administered (e.g. through state Boards of Pharmacy, DEA, other Federal or state systems, or privately, through a contractor established to administer the REMS)?**
General Comments
APhA recommends that education requirements for any REMS focus on effective use of the medication and patient safety. REMS education should also be verified and determined to be realistic, efficient, easily accessible and reasonably attainable so as not to be too burdensome on the prescriber or pharmacist, if such education is a required component of REMS. APhA also recommends that specific REMS education be provided and administered by accredited professional organizations that typically provide continuing medical education (CME) for prescriber or continuing education (CE) for pharmacists, that education be eligible for educational credit, and that educational components should be available free of charge to any willing prescriber that wishes to prescribe or pharmacist/pharmacy that wishes to participate and dispense medications requiring a specific REMS. Also, APhA expects that those pharmacists authorized to prescribe under certain requirements in their state through collaborative practice agreements would be required to meet the same requirements as other prescribers.

APhA also recommends that educational requirements be implemented as part of a standardized process where the verification of such education is seamlessly integrated into a system that is linked to and interoperable with existing medical and pharmacy technology and infrastructure, specifically, online electronic pharmacy claims adjudication systems. Seamless interoperability and validation would improve efficiency and workflow processes for pharmacists and for processing prescriptions because it would not require pharmacists to step-away from typical workflow to verify REMS requirements. In addition, verification procedures should be uniform across REMS.

Specific Educational Components
Related to specific educational components, APhA recommends that FDA ensure that educational materials and components for any REMS include:

- An explanation of why a REMS is in place.
- The risks to be mitigated, the reasons why such risks are targeted, and REMS elements/tools intended to address those identified risks.
  - **Specific for opioids** — educational materials should include information on why risks are associated with inappropriate prescribing practices and selection of non-opioid tolerant patients as it relates to abuse, diversion, misuse, and overdose.
- A brief therapeutic overview and a balance of risk and benefit information.
  - **Specific to opioids** — information should include tips for identifying non-opioid tolerant versus opioid tolerant patients, steps for appropriate opioid prescribing and dosage tapering/titration for initiation, maintenance and discontinuing of medication, signals or trends that might be related to risk of abuse/misuse/diversion, and what steps should be taken to address such risk issues identified by prescribers or pharmacists.
- A clearly communicated patient care plan and importance of a team approach between the prescriber, pharmacist and patient.
- Specific patient information that should be provided to the patient in order to be compliant with the REMS program and better ensure appropriate use of the medication and patient safety.
  - **Specific for opioids** — education information should also address proper storage, discontinuation, and disposal practices and why this is important to help prevent abuse, misuse, overdose, and/or diversion.
• Information on where the patient can access additional information.
• Clearly defined directions on which stakeholder is accountable for implementing/delivering each REMS component that is required.
• Clearly defined directions on which stakeholder is responsible for verifying that REMS components have been met, if required.
• REMS logistics — the processes and procedures required to prescribe, process (adjudicate), and dispense the medication to a patient.
  ▪ Specific requirements (education, training, documentation, other paperwork, laboratory orders/results, registration, etc.) that must be met in order to prescribe and dispense the medication(s) requiring a REMS.
  ▪ Options or steps for accessing and completing specific educational requirements, if required.
  ▪ Instructions on what will happen and directions on what to do (contingency plan) if a medication is prescribed but specific requirements of the REMS are not met (i.e. will a prescription be adjudicated/dispensed at the pharmacy if all requirements are not met ahead of time, or will there be a hard stop in the adjudication process requiring the pharmacist to address the issue and likely contact the prescriber, thus delaying the dispensing of the medication to the patient?)

Based on member feedback, nearly two-thirds said that such education elements should be included in an opioid REMS education program.

Verification
Specifically related to verification of pharmacy and/or pharmacist education, if required, FDA must consider that verification by pharmacy can be tracked by pharmacy identification numbers, such as the National Council for Prescription Drug Programs (NCPDP) Provider Identification Number assigned to every licensed pharmacy in the country, or the pharmacy National Provider Identifier (NPI) required by the Centers for Medicare and Medicaid Services (CMS). There are two examples of educational requirements currently being tracked by pharmacy, meaning the pharmacy attests that the pharmacists working in that pharmacy have been trained: 1) training required by CMS on fraud, waste and abuse, and 2) self-certification training required by the Drug Enforcement Administration (DEA) on sales of pseudoephedrine for purposes of combating methamphetamine abuse. In both examples, pharmacies maintain records of pharmacist training and submit verification of “pharmacy” training to the appropriate authorities to meet program requirements. We recommend that FDA consider such a model as an option to track/verify pharmacy/pharmacist education if required.

APhA recommends that any requirements for verification procedures of elements of a REMS, including educational/training requirements, registration, etc., be done through a standardized, real-time system-based approach that works for all REMS and that electronically/automatically checks against a REMS centralized database — triggered by a medications National Drug Code (NDC) through the pharmacy claims processing procedures. If a component of a REMS has not been met, we expect that an electronic message would be sent back to the pharmacy with a “smart message” describing what element(s) had not been met, and steps to address the issue. If an opioid REMS program is established that ties specific education and verification requirements to the Drug Enforcement Administration’s (DEA) registration and renewal process, APhA recommends that FDA clearly define how this requirement would be implemented for...
prescribers practicing in institutional/hospital practice settings who may not have their own unique DEA registration number; rather, they may use the facility’s general DEA registration number. Similarly, pharmacists typically do not have unique DEA registration numbers as DEA registration is required of the pharmacy, not the pharmacist, except those pharmacists who, where allowed, have met certain state requirements, obtained a unique DEA registration number, and are authorized to prescribe opioid medications through a collaborative practice agreement. Therefore, if there were requirements for pharmacist education that was tracked through DEA registration and renewal, FDA would have to clarify that such tracking be based on pharmacy DEA registration number, which would require that pharmacies to verify and attest that the pharmacists working in that pharmacy have been trained.

Regardless of the level of intensity of education and documentation/verification procedures that may be required for a specific REMS, APhA recommends requiring manufacturers to provide information on processes and logistics for a REMS program prior to implementation so that practitioners are aware for any REMS requirements prior to writing or dispensing a medication as part of a REMS program.

3) What education should be provided to patients, and should the system be designed to ensure such education is provided?

APhA supports increased focus on patient education and efforts to better ensure safe and effective use of the medication. Patient education and accountability is essential to achieve the intended outcomes of a REMS. APhA recommends that patient REMS education focus on the need to:

- Ensure that patient REMS education describes why a REMS is in place, what risks are intended to be mitigated, and what tools are being utilized for those specific purposes.
- Explain what information and/or procedures will be initiated and required of the prescriber and of the pharmacist.
- Include a clearly communicated patient care plan.
- Include information on specific patient responsibilities and patient accountability for meeting patient requirements for taking a medication that is part of a REMS program.
- Include information and directions for patients to complete specific requirements.
- Describe what to do if a physician-patient agreement is required and why it is in place.
  - **Specific to opioids** — if an agreement is required, APhA recommends that information clearly indicate who is accountable for verifying the agreement. In addition, we recommend that the pharmacy be informed of any such agreement, especially if the agreement includes direction on where and how often a patient fills their prescription. If pharmacists are aware of such an agreement, pharmacists can help prescribers manage their patients and work with prescribers regarding potential medication use issues.
- Indicate what patient educational materials should be provided by the physician and the pharmacist, if required, so that the patient is aware of any REMS requirements prior to arriving at the pharmacy. Ideally, patients should arrive at the pharmacy with education provided by the prescriber and be familiar with REMS requirements and next steps. It would be inappropriate for patients to first learn of any next steps or special requirements at the time of dispensing.
Ideally, the prescriber should provide directions for use, indication or intended use, intended length of therapy, and steps for initiating and discontinuing the medication (dose titrations).

- **Specific to opioids** — APhA recommends that patient information include recommend that information include why such information is important to help address identified risks (inappropriate use, non-opiate tolerance, abuse, misuse, overdose, and diversion) and the potential withdrawal symptoms that could lead to drug seeking behavior, which could lead to potential identified risks.

- Describe proper storage and disposal of the medication.
  - **Specific to opioid** — APhA recommends that patient information explain why these steps as so important in helping to prevent the unintended risks, especially diversion, which may be more prevalent at patients’ residences than they realize. Again, patient education and awareness is a key component in achieving the intended outcomes of an opioid REMS.

- Describe that a REMS program serves as an adjunct to, not a replacement of, prescriber/patient and pharmacist/patient dialogue about the benefits and risks of the medication. We recommend FDA consider how an expanded role of pharmacists could be better utilized to implement risk management programs and provide direct patient education through services such as medication therapy management services. Such services would require manufacturers to build in an appropriate compensation model into the specific REMS program for pharmacists and/or prescribers providing patient care services as part of a REMS.

Based on member feedback, nearly three-quarters of responders stressed the need for patient education to be part of any REMS program in order to achieve intended outcomes.

APhA also recommends that FDA utilize its existing health care provider and consumer communication tools to increase awareness of REMS programs, especially as new ones are rolled out. While APhA is willing to assist in getting the word out and educating pharmacist and student pharmacist members, we believe that the impact would be greater if FDA worked with and coordinate efforts with all stakeholders, including local, state and Federal agencies, to provide information and resources on public awareness, what any new REMS program means, and how it may impact prescribers, pharmacists and patients.

4) **Are other REMS elements necessary to support the safe use of approved opioids?**

APhA recommends FDA consider the following elements that we believe may be necessary to support the safe use of approved opioids targeted for an opioid REMS:

- Ensure that REMS programs allow any willing pharmacist, physician, other prescriber, or distributor the opportunity to participate.

- Ensure that any solution is not overly burdensome on the healthcare system and does not prevent or delay patient access to appropriate pain therapy. An opioid REMS should maintain appropriate access of pain medication for and use by pain patients with legitimate medical needs, not serve as a program focused on limiting access in order to address risks.

- Ensure that components of an opioid REMS are proven to be effective in mitigating the specific defined risks and are workable for patients, prescribers, pharmacists,
manufacturers, wholesalers, and system vendors. Outcomes (successes or failures) must be measureable and traceable to components implemented as part of opioid REMS.

- Ensure that a feedback loop is designed to allow continuous improvement by determining why patient failures occur or why opioid risks are not mitigated rather than just documenting the failure.
- Avoid potential unintended consequences of limiting health care provider participation in an opioid REMS due to educational requirements that may be too burdensome and thus limit pain patient access to pain medications requiring a REMS.
- Address the potential unintended consequences of shifting prescribing patterns from long-acting, extended release schedule II opioids to other pain medications such as shorter acting schedule III opioids, and the potential sub-therapeutic dosing for pain management due to such a shift, especially for chronic pain patients.

In addition, APhA recommends that FDA exempt medications that are prescribed for patients residing in long-term-care facilities, assisted living facilities, or hospitals.

Based on member feedback, the top responses of risks that an opioid REMS could address include: abuse, misuse, and use of high doses of long-acting and extended release opioid products in non-opioid tolerant or inappropriately selected patients. In addition, responders indicated the following components should be included as part of an opioid REMS: prescriber/pharmacist/patient education, and information on verification procedures.

B. System Issues

1) How restrictive a system should be designed? Is an [iPLEDGE] program/registry necessary for opioids? Given patient/health care system burdens and the number of patients, prescribers, and other health care providers involved, how would such a system be implemented?

APhA believes that an opioid REMS system should not restrict the opportunity for any willing prescriber, pharmacist/pharmacy, or distributor to participate. In addition, APhA does not support an iPLEDGE type program/registry for opioid REMS due to the significantly greater number of patients and number of prescriptions for the targeted opioid medications. As referenced in the Federal Register meeting notice, FDA acknowledges that in 2007 there were roughly 3.5 million unique patients receiving roughly 21 million prescriptions for the targeted opioids, a significantly larger impact than for isotretinoin in iPLEDGE. Due to economies of scale, it would be difficult to implement such a restrictive program without significantly impacting the health care system.

In addition, the medications, and thus risk management programs, are intended for significantly different patient populations, therapeutic intent, and risk mitigation. Also, the two programs are not parallel regarding the risk(s) intended to be mitigated. iPLEDGE is intended to mitigate one risk — pregnancy while on the medication. Whereas, an opioid REMS is intended to mitigate a variety of risks while taking the medication, including risks that may not be the result of the individual patient’s use of the medications, but rather non-patient use for non-medical purposes. Again, APhA is concerned that such a restrictive and time consuming program applied to opioids could have the unintended consequences of: limiting prescriber, pharmacist/pharmacy, or
distributor participation on the program; limiting patient willingness to participate in the program; shifting prescribing patterns to opioids not in the REMS; contributing to suboptimal pain care; and contributing to increased rates of risk associated with opioids not in the REMS.

Implementation of a REMS system is discussed in Question B3 below.

2) **Should the REMS include controls on distributors who distribute products to pharmacies/others? What controls are necessary, and how can they be efficiently provided without being unduly burdensome on the health care system?**

APhA does not support potential requirements for distributors/wholesalers to verify that REMS components have been met prior to shipping stock medications (similar to iPLEDGE and/or restricted distribution systems). Such procedures are burdensome on the distribution system. Prior verification to shipping medications could also lead to delay in patient access or disruption of patient treatment regimens if a pharmacy does not have stock to dispense but all other requirements of a REMS program have been met. Additionally, we believe that there should be a standardized mechanism in place for REMS that can easily reconcile dispensing records with shipping records from a distributor to a pharmacy for purposes of surveillance.

**Related to opioid REMS** — we believe that specific restrictions on distributors pursuant to a REMS is not required and would have limited benefit. Distributors already have procedures and systems in place to meet DEA reporting requirements and must monitor customers’ orders of controlled substances — to identify those that might fall “outside” the normal ordering patterns and amounts for the customer. We encourage FDA to recognize monitoring systems that are already in place and not require additional restrictions on wholesalers. However, if there is a restriction requirement for a REMS, wholesalers would need access to the REMS system/database (described in Question B3) in order to meet distributor requirements.

Based on member feedback, nearly 40% said that verification procedures by wholesalers prior to opioid REMS product shipment should be avoided.

3) **What existing systems (for example, in pharmacies) already exist that could be used to implement a REMS?**

APhA recommends that FDA work with manufacturers and stakeholders, including pharmacy, on the development of one REMS process that can be utilized for all medications requiring a REMS, thus limiting the silo effect of risk management programs. APhA supports a standardized, system-based approach with standard components selectively utilized based on the intensity of the required REMS. Such a system would serve as a way to address the challenges pharmacists face with the existing risk management programs that lack standardization or consistent components. The lack of standardization is inefficient for practice workflows, time consuming and a burden to the overall health care system. Given the growing number of medications that require a REMS, in addition to the novel systems already required, and the number of prescriptions for REMS medications now and in the future, we are extremely concerned that if a standardized system is not implemented then prescribers and pharmacists may limit their participation in the program(s), which could lead to reduced patient access.
While a specific REMS solution may not be identified yet, there are options. Systems are in place that can be connected to or otherwise interoperable with existing standardized, electronic, real-time pharmacy claims adjudication infrastructure, which is why we think it is important that a REMS solution be interoperable with existing health information technology and systems. In addition, any solution needs to accommodate the varying ways that prescriptions are received at the pharmacy (i.e., hand-written, fax, telephone, electronic prescribing, and electronic health records).

**General REMS Recommendations**

APhA offers the following general recommendations regarding REMS programs:

- APhA strongly believes that the best way for FDA to proceed with REMS is to ensure that a standardized, system-based approach is developed for REMS that allows for a single “entry point” for implementing and managing all REMS. In addition:
  - A REMS system should be interoperable with existing and/or future health information technology and electronic/online infrastructure, specifically, all medical records and pharmacy management systems, including the utilization of electronic prescribing and electronic health records;
  - A REMS system must integrate seamlessly into practice workflow for physicians, other prescribers, and pharmacists, and ensure that administrative steps and procedures are minimized for verification (checking) that REMS requirements have been met;
  - A standardized REMS approach should be useful and workable for any future drugs and drug categories that require a REMS; and
  - A REMS program should not interfere with patient access to medications.

- APhA strongly recommends that FDA ensure that the components of REMS are proven to be effective in mitigating the specific defined risks and are workable for patients, prescribers, pharmacists, manufacturers, wholesalers, and system vendors. In addition:
  - Administrative burden should be limited for all stakeholders; and
  - REMS programs must clearly define the stakeholder accountable for documenting and implementing each REMS component and ensure that the patient is an integral part of the education process.

- APhA strongly recommends that standardized REMS program components/elements should be developed. Standardization of REMS components would decrease burden and confusion, improve efficiency, and limit potential implementation and management glitches in the system. For example, obtaining and completing educational requirements, if required, could be a standard process for each REMS (i.e., online module with online submission) so that stakeholders are not asked to do something different for each REMS.

- APhA recommends FDA consider restructuring the REMS programs so that REMS are designed by levels of intensity based on standardized set of REMS components that would be required in different levels, or “schedules”, of programs. Designing and implementing a REMS for certain opioids gives us the opportunity to create a standardized, system-based solution with standard components selectively utilized based on the intensity of any required REMS. For example, using the DEA model for schedules of controlled substances, a “Level 1” REMS could be the most restrictive REMS with the most components; a “Level 5” REMS could be the simplest REMS with fewer components and less burden. Regardless of how such a system was labeled (schedules, alpha letters, or color scheme), the structure of each
level could be consistent — a standard set of requirements and components that would be part of a specific level. Thus, a “Level 1” REMS for one drug would have the same components and requirements as another “Level 1” drug, the differences would be specific to the risks to be mitigated. Given the growing number of REMS, such a system may help to standardize the process, allow stakeholders to be familiar with what is required of different levels of REMS, and could provide stakeholders with consistency and awareness for what is expected with different levels, and could serve as a quick reference guide for what is expected for different REMS.

• Prescribers and pharmacists must be compensated [via manufacturer(s)] for the time required to implement, manage, and counsel patients related to a specific REMS medication. Specific for pharmacists, such an encounter could be considered a provision of medication therapy management.

Current Standardized Process
In the past, APhA worked with the Centers for Medicare and Medicaid Services (CMS) to help design an optimal prescription processing solution for Medicare Part D that worked for pharmacy and our patients that is accessible by all of pharmacy. We are prepared to work with FDA and stakeholders to design and implement an optimal system and solution for opioid REMS. Only through a public-private partnership with FDA, manufacturers, pharmacists, physicians, other prescribers, and wholesalers at the table can a standardized and meaningful REMS system succeed.

REMS ComponentsOutlined by FDA
To better ensure success of any REMS, APhA offers the following recommendations for existing provisions that could be part of a REMS program (as outlined by FDA in the Federal Register notice; bulleted in italics below) and additional provisions that APhA believes should be components of a risk management system and interoperable infrastructure:

• Every REMS must include a timetable for REMS assessment.
  o APhA recommends that FDA ensure that this existing provision allow for a REMS to be revised or “fine-tuned” based on post-implementation, surveillance, and quality assessment data. Such revision would allow for components of a REMS that, based on assessment show little if any measurable effectiveness/success, or are too burdensome/challenging, to be revised or removed as a component of a REMS. Likewise, successful components could be further enhanced and emphasized.

• A REMS may include a MedGuide, patient package insert, a communication plan, and certain elements to assure safe use.
  o APhA recommends that FDA better define how it intends to use this existing provision due to ongoing concerns with the dispensing of patient information in the existing MedGuide and patient package insert formats.
  o FDA and stakeholders, including APhA, have had many discussions during the last several years regarding challenges related to MedGuides and the need for improvements. While we appreciate FDA’s understanding and acknowledgement of the challenges, no change has been implemented and challenges remain.
Challenges include: Increasing number of MedGuides; lack of evidence showing effectiveness; lack of standardization; lack of details used for determining the requirement of a MedGuide; confusion and lack of consistency with other patient information; workflow inefficiencies; supply/availability; transfer of printing costs to from manufacturer to pharmacy; lack of balanced information; and health literacy/readability.

- Given the ongoing challenges, APhA is concerned that MedGuides are a “go-to” tool for REMS, even for opioid REMS.

- APhA recommends that FDA utilize its focus on REMS to address MedGuide challenges. Specifically, we recommend that FDA act upon recommendations voted on by the FDA Risk Communication Advisory Committee (February 27, 2009) to improve/combine all patient information into one standardized, easy to read document utilizing the “Drug Fact” box format before approving any new REMS requiring a MedGuide as the patient information tool. A complete list of recommendations from the Committee is included on pages 1-2 in the Executive Summary of the meeting minutes, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/UCM152593.pdf.

- Elements to assure safe use must include goals to mitigate a specific serious risk listed in the labeling of the drug, which may include the following requirements:
  - Prescribers to have particular training/experience or are specially certified.
    - APhA appreciates the need for additional training and education on specific medications. However, we are concerned that there is not a standardized approach for determining when specific educational requirements will be required as part of a REMS and to what degree of information/training any given education requirement may require.
    - APhA recommends that as part of FDA overall REMS focus, FDA ensure that there is a standardized approach to developing, providing and verifying specific educational requirements have been met.
  - Pharmacies or other dispensers to be specially certified
    - As just described under prescriber training/experience, the same concept applies for pharmacists. However, it is important to note that verification of pharmacy varies from verification of pharmacists due to the lack of a nationally recognized/standard pharmacist identification. Until such a model or requirement exists, tracking by pharmacy may serve to be a more useful process and efficient process if specific certification/training is required.
  - Restricted distribution by certain settings
    - While APhA appreciates the potential need for programs that restrict distribution of a product to ensure its safe use, we caution against developing systems that may arbitrarily limit health care provider participation or limit patient access to these medications through overly burdensome requirements.
    - APhA recommends that any willing prescriber, pharmacist or pharmacy have the option to participate in any restricted distribution system that may be a requirement for a REMS. However, APhA considers such restriction
to be the highest level of mitigation strategy for a REMS; we caution against its overuse.

- **Dispensed to patient based on safe use conditions, such as lab results**
  - APhA recommends that safe use conditions, such as lab results, be specifically defined in a REMS program which provider is responsible for ordering, interpreting, documenting, and verifying lab orders and results have been completed, or other such provisions required by a REMS.
  - APhA recommends that pharmacists have HIPAA compliant and appropriate access to or verification of lab data for a REMS through a standardized process workable for any REMS requiring the use of lab data.

- **Patient monitoring**
  - APhA recommends that patient monitoring provisions within REMS programs be standardized as to how they are implemented/document and clearly define the provider accountable for such provisions. In addition, we recommend clearly defining the risks to be mitigated and outcomes to be measured through patient monitoring.

- **Patient registry**
  - APhA recommends that patient registries only be implemented for the most restrictive REMS programs where specific patient monitoring, documentation, or lab test are required. In addition, such a program must outline which provider is responsible for registering and verifying a patient has been registered, and that the patient has been educated on the REMS program/responsibilities. APhA recommends that patients receive initial information, education and registration by the prescriber that would be supplemented by information received from the pharmacist at the point of dispensing.

- **May include an implementation plan where sponsor monitors, evaluates, and works to improve implementation of these elements**
  - APhA recommends that any implementation plan include a clearly defined feedback loop for capturing outcomes and communicating with a sponsor regarding implementation challenges that may arise. In addition, any implementation plan should clearly define who is responsible for implementing specific components and include a detailed timeline/plan for assessment/action on any implementation challenges.

**Pilot Program**
- APhA recommends REMS be pilot-tested prior to implementation so that any glitches can be resolved prior to a nation-wide launch of the program. APhA also believes that a pilot program would help determine if elements of a REMS are effective at mitigating identified risks (similar in concept to recruitment for and implementation of label comprehension studies in prescription to over-the-counter switch applications from manufacturers). Based on member feedback, nearly three-quarters said that a pilot program would have improved the implementation of exiting risk management programs. Given the challenges that pharmacies have with existing risk management programs, we believe that pharmacies could be identified that
would be willing to participate in a pilot program to ensure a smoother nationwide implementation.

- **Specific to opioid REMS**, a pilot program would be especially important given the significantly greater number of prescriptions, patients, and other stakeholders involved compared to other risk management programs, such as iPLEDGE.
- Based on member feedback, nearly all said that a pilot program for opioid REMS would be beneficial prior to nation-wide implementation.

- **Generally, innovator and generic sponsor shall use a single, shared system**
  - As in Question B4 below, we support this provision and encourage FDA to continue to require a single, shared REMS system both brand/innovator and generic sponsors if a REMs is required.

**4) FDAAA requires that innovator and generic sponsors use a single, shared system to provide a REMS with elements to assure safe use. What obstacles need to be addressed before such a system could be developed?**

APhA strongly supports the FDAAA requirements that innovators and generic sponsors use a single, shared system for a REMS program. Such a process is beneficial for prescribers, pharmacists, pharmacies, wholesalers, and patients because it decreases confusion and/or burden of implementing different programs for the same product. As this process evolves, we recommend that FDA ensure the following issue are addressed: that any REMS program include specific and accurate information on equivalency of the brand and generic product and if there are any restrictions on substituting one product for the other, for example, after the patient has started the brand or generic version of the medication.

**5) What metrics should be used to assess the success of the REMS?**

APhA supports FDA’s interest in using metrics to measure REMS outcomes (successes or failures) and on quality improvement provisions. APhA recommends that efforts used in creating a REMS are equally matched by efforts to evaluate the effectiveness/outcomes of a REMS and its individual components. FDA must ensure that the components of any REMS are proven to be effective in mitigating the specific defined risks and are workable for patients, prescribers, pharmacists, manufacturers, wholesalers, and system vendors. In addition, we recommend:

- Monitoring and evaluating program compliance/outcomes on effectiveness at the patient, prescriber and pharmacy level by using the functionality of a standardized, system based REMS model.
- Defining specific outcome and parameters intended to be measured prior to implementation, matched to an effective evaluation method, and pilot testing for effectiveness.
- Designing a feedback loop as part of a standardized, interoperable REMS system to allow continuous quality improvement by documenting and determining why a patient failure occurred, rather than just documenting the failure. The system should also capture and be able to report on the frequency of components of a REMS not being met and what those
components were, delays in patient access due to components not being met (compliance of a REMS program), and the number of prescriptions being dispensed that require a REMS.

- Allowing REMS programs to re-evaluate, assess and adjust, including discontinuing, throughout the lifecycle of the REMS.
- Requiring REMS programs to include information on where and how to report adverse drug events, identified risks, and failures of a REMS program/components, such as FDA’s MedWatch program.

**Specific to opioid REMS**—APhA recommends that FDA clearly define the outcomes and metrics to be measured that will capture success or failure of a program. In addition, we recommend requiring manufacturers and FDA to indicate what REMS components are being utilized to address a given risk so that metrics can be established/utilized to measure success or failure of those tools. We also recommend FDA explore ways to coordinate with and utilize existing tracking and reporting processes and requirements, such as state prescription drug monitoring programs (PDMPs), as a way to contribute to FDA’s efforts.

Finally, an opioid REMS will likely contribute to success in addressing opioid risk as part of a collaborative effort, not as a stand-alone program to address a growing public health issue. Unfortunately, for opioid REMS, the identified risk of abuse, misuse, diversion, and unintentional/intentional overdose are measures that may fall outside the medical use of the medication and/or outside of the actual use of the medication by the patient. Ultimately, we should expect that education of prescribers and patients should show a reduction in the identified risks. However, linking outcomes of specific educational tools, interventions or programs with public health success or reduction of these risks is challenging. APhA is willing to work with FDA and stakeholders to ensure that as an opioid REMS is defined, we utilize tools that will limit burden on the health care system but provide the solution and outcomes needed to address opioid risks.

Thank you for the opportunity to provide comments on this important issue, on which we look forward to continuing to work with the Agency. If you have any questions or require additional information, please contact Marcie Bough, Director of Federal Regulatory Affairs, at (202) 429-7538, or at mbough@aphanet.org.

Sincerely,

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