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by D. Woods

SUMMARY

The FDA is not impressed with industry's proposals for opioid risk management. ♦ The FDA will hold an advisory meeting sometime in spring 2010. ♦ The industry proposal is for a phased-in risk management program over several years, but the proposals appeared to be weaker – focusing on patient medication guides, letters to healthcare practitioners, and voluntary training – than the FDA would like. ♦ Industry also wants to link physician training to physician Drug Enforcement Agency (DEA) certification, which would be a daunting task because Congress would have to pass a law requiring it and because strong opposition is expected, even from the DEA itself.

Trends-in-Medicine
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FDA Public Meeting on Opioid Risk Management

College Park, MD
December 4, 2009

On December 4, 2009, the FDA held a public meeting with manufacturers of long-acting (LA) and extended-release (ER) opioids on the progress they have made in developing a Risk Evaluation and Mitigation Strategy (REMS) for these drugs, and the Agency did not appear very happy with what they heard. There were fewer details than the FDA expected, the proposals were rather weak, and an industry call for further involvement of the Drug Enforcement Administration (DEA) got a cool reception.

A coalition of the pharmaceutical companies which manufacture these opioids – the Industry Working Group (IWG) – submitted a ***revised*** draft REMS to the FDA, calling for a phased REMS approach. The IWG members gave an overview of their meeting with stakeholders in November 2009 and explained why they revised their draft REMS. The IWG said that stakeholders told it that the original draft REMS would interfere with access, place a burden on the healthcare system, drive abuse to other drugs, drive doctors out of pain management, and cause a public health crisis. It said that the scope of the REMS "represents an unprecedented interference with medical practice and an infringement of human rights."

It was clear that if there is a consensus on the part of the IWG and stakeholders, it is to resist change and only implement the most benign parts of a REMS – education and information. One IWG speaker argued that it would be virtually impossible to test the REMS and asked the FDA for definitions of abuse, misuse, addiction, and overuse, saying that no progress could be made unless those four words were defined.

The new IWG proposal starts with patient medication guides, Dear Healthcare Professional (HCP) letters, and voluntary training for physicians. The IWG said that it is against mandatory training or certification and warned that doctors would opt out of prescribing long-acting or extended-release opioids if a strict REMS is instituted. However, several FDA panel members indicated that they favored mandatory physician training as part of the REMS.

The IWG also proposed linking training and certification to a physician's DEA certification, which would require an act of Congress. Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, Center for Drug Evaluation and Research (CDER), raised his eyebrows at that idea. He said that state medical boards had told the FDA that they thought any relationship with the DEA would be a bad idea.

The IWG presentation was followed by about two hours of questioning by FDA members, who also read questions from the audience. The meeting, which was relatively short, consisted of 15 FDA members and five industry representatives

(three from Roxane Laboratories, 1 from Johnson & Johnson, and 1 from King Pharmaceuticals).

FDA officials on the panel said that the plan looks more like a pre-FDA Amendment Act (FDAAA) risk management plan – an older, weaker risk management approach – than the type of REMS the FDA is seeking. FDA panel members also noted that the IWG asked more questions than it answered. While most FDA panel members stared blankly during the more than four hour meeting, several expressed concern that the IWG was short on details.

After the session, Dr. John Jenkins, director of the FDA's Office of New Drugs (OND), CDER, said that he thought that progress had been made. Jane Axelrad, associate director for policy in the FDA's Center for Drug Evaluation and Research, said that she would have liked to have seen more specifics from the IWG.

Background

On February 6, 2009, the FDA told manufacturers of some specific opioid drugs that those drugs would be required to have a REMS to ensure that the benefits outweigh the risks associated with:

- Abuse.
- Use of high doses of LA/ER opioids in non-tolerant and "inappropriately selected" people.
- Misuse.
- Overdose, both accidental and intentional.

Opioid Products that May Be Required to Have a REMS

Generic name	Product name	Manufacturer
Brand opioid products that may be required to have a REMS		
Fentanyl	Duragesic ER transdermal system	Johnson & Johnson
Hydromorphone	Palladone ER capsules *	Purdue Pharma
Methadone	Dolophine tablets	Roxane Laboratories
Morphine	Kadian ER capsules	Actavis
Morphine	Avinza ER capsules	King Pharmaceuticals
Morphine	MS Contin ER tablets	Purdue Pharma
Morphine	Oramorph ER tablets	Xanodyne Pharmaceuticals
Oxycodone	OxyContin ER tablets	Purdue Pharma
Oxymorphone	Opana ER tablets	Endo Pharmaceuticals
Generic opioid products that may be required to have a REMS		
Fentanyl	Fentanyl ER transdermal system	Actavis
Fentanyl	Fentanyl ER transdermal system	Lavipharm Labs
Fentanyl	Fentanyl ER transdermal system	Mylan Technologies
Fentanyl	Fentanyl ER transdermal system	Teva Pharmaceutical Industries
Fentanyl	Fentanyl ER transdermal system	Watson Pharmaceuticals
Methadone	Methadone tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Novartis/Sandoz
Morphine	Morphine sulfate ER tablets	Endo Pharmaceuticals
Morphine	Morphine sulfate ER tablets	KV Pharmaceuticals
Morphine	Morphine sulfate ER tablets	Mallinckrodt
Morphine	Morphine sulfate ER tablets	Watson Pharmaceuticals
Oxycodone	Oxycodone ER tablets **	Impax Labs
Oxycodone	Oxycodone ER tablets	Mallinckrodt
Oxycodone	Oxycodone ER tablets **	Teva Pharmaceutical Industries

*** No longer being marketed, but still approved. ** Discontinued**

In March 2009 and again in May 2009 the FDA held meetings with sponsors, healthcare professionals, patient advocates, and pharmacy groups to discuss an opioid REMS. A public meeting was held on May 27 and 28, 2009, with nearly 100 members of the public speaking. During this public meeting, only FDA staff were able to question the companies. However, members of the public were given index cards on which to write suggested questions.

On October 19, 2009, the FDA re-opened for one year the docket because of the huge number of submissions.

The FDA Perspective

Dr. Jenkins said the FDA remains committed to implementing a REMS for long-acting and extended-release opioids, "The FDA recognizes the value of opioid analgesics…We also recognize that despite previous efforts to mitigate the risks associated with these products, serious adverse outcomes continue to increase. It is essential that we try to find a way to ensure that the overall benefits of these drugs continue to outweigh the risks...In February of this year, we notified the sponsors that a REMS would be required for long-acting and sustained-release (SR) opioids."

Dr. Jenkins is the chair of a steering committee that oversees seven groups working on REMS and that over the past several months those working groups have been meeting regularly, "This is a significant task, and we are working deliberately…There has been some confusion regarding the implications of the re-opening of the docket and the closing date. The extension…is not tied to any timeline for a REMS decision by the FDA or implementation. We continue to review all public and stakeholder input, and we will consider additional extension of the comment period (when) we feel there is a need to do so." Dr. Jenkins said that the FDA is considering dates in spring 2010 for a public advisory meeting on this topic.

THE IWG PERSPECTIVE

Dr. Susan Nicholson of Johnson & Johnson, who gave the IWG overview, said that this was the first IWG meeting with the FDA. She said a consensus is being sought but may not be possible, and there will be votes on key issues. The IWG, which formed in late March of 2009, created several sub-teams: operations (to manage the consortium), regulatory/ communications, dispenser, prescriber, patient, metrics (to ensure that the impact of programs can be measured), and technology.

Stakeholders include the Federation of State Medical Boards (FSMB), government agencies, pain and addiction treatment communities, patient and consumer advocates, pharmacists and dispensers, prescribers, professional societies, and state licensing boards. The Pain Care Forum has a group which is specifically working on REMS, and the IWG met with it on September 17, 2009, to talk about REMS draft objectives, HCP certification or particular training with an outline of education topics, dispenser education, patient education, and the use of patient-prescriber agreements (PPAs).

The IWG met with the DEA on October 6, 2009, to talk about its involvement in developing a REMS. The IWG wanted to know if the registration process could be changed so that specific opioid education would be required to get a DEA number. The DEA said that it would take an act of Congress to change the way the registration process works regarding the DEA.

On November 18, 2009, the IWG met with stakeholders, including 36 societies and advocacy groups, to discuss the draft REMS. The FDA sent two observers. Dr. Nicholson said that the feedback at the meeting was "loud and clear. The stakeholders told us that universal prescriber certification, if onerous, would…lead them to opt out." She said that the scope of the REMS would affect:

- Around 1 million DEA registrants.
- 680,000 active MD or DO registrants.
- 28 million prescriptions per year of long-acting opioids.
- 4 million patients.

Dr. Nicholson cited numerous differences between the previous REMS and the ER/LA opioid REMS including the focus, the number of risk factors, the target audience and the size of that audience, and elements to assure safe use (ETASUs). She said that stakeholders told the IWG that the proposed REMS had the potential to hurt patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing healthcare (such as patients in rural or medically underserved areas). The most concerning part of the plan was the "onerous" certification requirements for prescribers.

Dr. Nicholson said the IWG has worked diligently to develop a draft REMS proposal. It presented its draft REMS proposal to more than 40 stakeholder groups and received significant pushback. Based upon this feedback, she said IWG is proposing an alternative approach.

Proposed draft REMS

Greg Hicks, PharmD, of Roxane Laboratories presented the draft REMS that was presented to the stakeholders on November 19, 2009, emphasizing that education was the key.

Considerations for LA/ER opioid REMS:

- **Medication Guide:** Each manufacturer would supply a product-specific medication guide in accordance with 21 CFR 208.24 to ensure that every patient who is dispensed a prescription will have access to it.
- **Communication Plan:** Could include web-based information and letters to HCPs to support the REMS.
  - Dear HCP letters explaining REMS and what specific risks are intended to be mitigated:
    1. New requirements for prescribers.
    2. New recommendations for patients.
    3. Access to traditional information.
    4. Recognition of possible misuse, abuse, addiction or overdose and what actions should be taken.
    5. Reminder to distribute the guide.
  - **Prescriber training or certification:** Five key educational goals for prescribers should include proper patient selection and the need to educate patients on proper use, storage, and disposal of the products.

Dr. Hicks said that prescribers of the affected drugs can be divided into two groups: Those who need particular training and those who need special certification. Prescribers who need particular training need educational programs that should be tested. Completion of REMS education programs should qualify prescribers for advanced education credits. He said that neither government nor industry "should dictate the detailed content of training programs, nor should they directly conduct the certification of prescribers in the safe use, storage, and disposal of opioid analgesics…If the FDA requires verification of particular training or certification by the dispenser before dispensing, our recommendation would be to create a mechanism, analogous to the mechanism for a modifier to DEA registration numbers created by the Drug Addiction Treatment Act of 2000, that allowed the prescribing of buprenorphine for the treatment of addiction to opioids… Using the DEA certification (which would be phased in over three years) would not create a great burden on prescribers."

Under this proposal, prescribers with "special certification" (i.e., by a professional board) could be exempt from the particular training if the previously mentioned criteria are met as part of their special certification. As far as dispenser certification, the IWG "does not recommend a specific certification requirement for individual pharmacists to dispense certain

opioids. However, REMS-related information will be made readily available to all pharmacists."

Regarding patient education, Dr. Hicks said that:

- All items should be tested for comprehension in appropriate audiences.
- All items should be tested for literacy level, and icons may be used.
- Translation may be necessary from the beginning – Spanish at a minimum.
- A patient-prescriber agreement could be read and signed.

The IWG created a draft patient-prescriber agreement describing the risks and benefits of the drugs. Terms such as narcotic and controlled substances were avoided in the draft agreement. The IWG also created a Patient Medication Information Sheet (PMIS) describing the benefits and risks of the drugs which would be non-product specific. The proposed PMIS would emphasize class-specific information and would include a wallet card. Dr. Hicks said that the IWG also is working on web-based informational materials for prescribers, dispensers, and patients/caregivers.

The FDA's Dr. Jenkins asked about linking training certification with the DEA. Dr. Nicholson said, "My introduction was a summary of what we've done to get to where we are today, so we created a draft REMS, shared with stakeholders. We have significantly revised the plan with some of the important elements, certification being one of them, but we wanted to show you what we had shown to stakeholders."

The FDA's Axelrad asked, "How many people who prescribe or receive these medications don't have access to the internet?" Dr. Hicks responded that a lot of patients are in very vulnerable populations, "They can be poor, elderly, and they may not have the skills to negotiate internet access, so that's one of the issues we are looking at. We got a lot of pushback on that." The FDA's Axelrad added, "It's important to know how many of these people need to be reached."

Proposed REMS metrics

Dr. Sidney Schnoll of Pinney Associates gave an overview of the REMS metrics – how the plan would be assessed, "They are quite complex, and this can be a bit of a bumpy ride, so I ask all of you to fasten your seatbelts…The bottom line is that the REMS should not impede access…for patients."

Proposed REMS assessment:

- At defined time points (i.e., 18 months, 3 years, 7 years), we will assess the extent to which each of the REMS elements and the REMS as a whole are meeting program objectives and whether modifications are needed. Any changes would need to be documented and accounted for.
- Currently, there are no standard definitions for the terms misuse, abuse, overdose, and addiction. There is no consensus. This needs to be addressed as soon as possible, and there should be consensus on all levels of the definitions. Dr. Schnoll said, "Many of the stakeholders at the November meeting thought this was vital…It has not been clarified whether overdoses include fatal and non-fatal poisoning…There can be no REMS evaluation until the agency defines what they intended when they used these terms."

Dr. Schnoll said it would be "disingenuous" to attribute lower levels of misuse or abuse to a REMS, "Addiction leveled off between 2002 and 2008, suggesting that broader societal factors are affecting (misuse/abuse)…even before institution of REMS…The very nature of our drug addiction treatment

REMS Measurement Issues

Previous REMS	Proposed ER/LA opioid REMS	Measurement issues
Single drug focus	Multiple active ingredients and formulations	Addressing drug specificity at many levels (e.g., class, formulation, active ingredients) Assessment of impact on short-acting and long-acting opioids
Usually addressed one or two risks (usually physiological)	Multifactorial risks (e.g., social, genetic)	Should consider how non-pharmacological risk factors will be accounted for in determining effectiveness of the REMS
Addressed one or two outcomes	Multiple outcomes (abuse, misuse, addiction, fatal overdose)	Determine whether separate mitigation and evaluation strategies are needed for each outcome
Intended to reduce risks in patients	Intended to reduce risks in patients, with possible impact on non-patients	Identifying the acceptable level of events in non-patients Determining the balance between measuring outcomes in patients vs. non-patients
Relatively small patient population	Large number of patients and prescribers 4 million patients 1 million registrants 28 million prescriptions	How to measure individual exposure to the REMS Assessment of the impact on the healthcare system Determining the value of data from small focused studies vs. national data Identifying the most appropriate mechanism to measure patient knowledge of risks and drug storage/disposal behaviors
Elements to assure safe use (ETASUs) applied in the minority of REMS. Relied mostly on Medication Guides and communication plans	Complex elements beyond Medication Guide. ETASUs would have to be applied to many different specialized and general care patient groups and several different physician specialties as well as primary care providers	Determining whether each element should be evaluated individually Assessing whether each element should be evaluated with phased approach

may change dramatically in the coming years…These long-term epidemiologic trends need to be accounted for in the final analysis…Attributing anything solely to the REMS would be dishonest."

He explained that three types of data are needed in order to measure the REMS success:

- **Pre/phase-in testing:** Do REMS elements and materials function as intended? (This would require comprehension studies of printed materials, feasibility assessments, and demonstrations)
- **Monitoring:** How are the REMS being instituted (process measures, rate, and number of prescribers certified)?
- **Evaluation:** Has the REMS achieved its intended results (on the patient population, changes in patient knowledge and behavior, on the healthcare system)?

Dr. Schnoll said that it is necessary to determine the REMS' impact on pharmacists and to look at unintended consequences of the REMS, including impact on short-acting opioid and over-the-counter (OTC) pain reliever use patterns and abuse. He also warned against setting the standard too high, "The bottom line…is to affect the behavior of all stakeholders… There is no simple measure to determine if all this activity will result in a change in behavior."

As for timing of data availability, Dr. Schnoll said, "(At 18 months) only limited information on changes in rates of adverse outcomes will be available…There already appears to be a leveling off of drug use…There have already been major changes at hospitals…which may make long-term assessment of data difficult."

He concluded:

- The scope of the draft REMS is unprecedented in its size, complexity, and reach.
- At this time data collection systems do not exist to gather data deemed important by every stakeholder.
- It will be difficult to predict all of the unintended consequences, yet every effort must be made to anticipate as many as possible to make sure the REMS doesn't create more problems than it addresses.
- The final structure of the REMS is unknown.
- REMS will be iterative, and changes must be accounted for in any evaluation.

The FDA's Axelrad asked for the data demonstrating the leveling off of non-medical use and abuse. She wanted specific numbers. Dr. Schnoll stated that the data were from the National Survey of Drug Use and Health (NSDUH) and that he would include it in the docket.

The FDA's Dr. Jason Woo, associate director for Scientific and Medical Affairs, Office of Compliance, CDER, commented that there were no specifics presented at the meeting regarding a REMS. Dr. Schnoll responded, "To talk about compliance is difficult…Once we get things set up and approved, there will be compliance by all stakeholders." Dr. Woo asked how difficult that has been in terms of coming to a consensus. Dr. Schnoll said that the IWG has been working very cooperatively.

Dr. Sharon Hertz, deputy director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, said that the IWG had a lot of questions and asked, "Do you have any answers?" Dr. Schnoll replied, "At this point we are investigating various directions that can be taken, but nothing is certain." Dr. Hertz asked, "Are you waiting for us to answer those questions, or do you have any proposals? Has the group generated any independent thoughts? It would be very helpful to have you present that rather than just pose questions if you have discussed and worked in those areas, instead of asking us a lot of questions."

The FDA's Axelrad added, "I share Sharon's frustration, and every one of these questions could be turned back. We would like to see what the industry is proposing in terms of basic metrics and elements of the REMS. Maybe you will get to that in the next presentation. We want to see what you think are the basic set of measurements (that) are possible...I'm sure that there are some basic measurements and basic data sets that we know now that can be looked at." Dr. Nicholson responded, "In terms of the specific REMS plans that we are proposing, that will be the next discussion."

Proposed REMS feedback

Eric Smith, PharmD, of King Pharmaceuticals discussed the feedback the IWG heard at the November 2009 stakeholder meeting in Washington, DC. This feedback included:

- The first priority is "do no harm."
- Draft REMS is expected to interfere with access, burden the healthcare system, and drive abuse to other drugs ("balloon effect").
- REMS could limit access to the underserved and cause a "public health crisis."
- "Do everything possible to avoid unintended consequences."
- The scope of this REMS represents "an unprecedented interference with medical practice and an infringement of human rights."
- Stakeholders asked to be active participants in the development of the REMS.

He said the unintended consequences of the REMS would mean decreased access to pain medications for legitimate medical purposes, a shift in prescribing to opioids not covered by the draft REMS and other pain medications, doctors opting out of pain care due to burdensome certification requirements, particularly in rural areas, which would disproportionately affect the poor, people of color, and women. He added that

mandatory training or certification that gives prescribers the option to opt out is a potential problem as this may decrease the available prescribers, limit patient access, and increase the burden of prescribers who opt in. Thus, prescriber training should be included but not mandatory as a condition for prescribing. If training can't be voluntary, he said a voluntary initial phase leading up to required training should be the approach. Training curriculums should be guided by societies and not industry, he added.

Stakeholders discussed three REMS recommendations that would involve Congress:

1. Informational campaign to inform patients of the impending REMS, so they can interact with their congressional delegates.
2. Drafting legislation to amend the FDAAA.
3. Drafting an amendment to the Controlled Substances Act (CSA).

Dispenser perspective

- The REMS should not include components that delay or prevent patients from getting their prescribed medication.
- Pharmacists do not support doing any manual checks of prescriber compliance and do not want a separate medication guide for every opioid.
- Pharmacist education is important and should be highlighted more in the REMS but should not be mandatory.
- Training curriculum should be standardized so multiple groups could offer it.
- A modular approach to educational materials was recommended.

Patient perspective

- There is a concern that prescribers are not taking time to appropriately educate patients.
- Current educational materials are inadequate. The IWG recommended creating a packet so that patients can be educated over time with different training materials.
- The patient-provider agreement is too long and too one-sided.

Metrics issues

- Measuring the simplest things that can be measured, including medication guides, patient medication information sheet distribution, knowledge surveys, number of prescribers opting out, changes in prescribing patterns.
- Using a phased approach because otherwise it would not be possible to determine which of the various components are having an effect.
- Obtaining a consensus with the FDA on definitions of abuse, misuse, overdose, and addiction.

Stakeholder recommendations

- ***Prescriber training or certification.*** No prescriber registries and no training or certification as a requirement for prescribing that allows prescribers to opt out.
- ***Train everyone.*** If evidence of training is required, stakeholders endorsed linking it to the DEA registration renewal process.
- ***Phase in the REMS program.***
- ***Educate each group about what their responsibility is.*** Education/training should be done by stakeholders, and the curriculum should be standardized.
- ***Endorse a voluntary prescriber training program*** to assess the impact on prescribers and effectiveness of the training, modifying as appropriate.

Revised Draft REMS

Dr. Smith presented the revised draft approach to the REMS and highlighted these changes to the IWG's approach:

- Implementing a class-wide REMS (immediate action) containing components that can be instituted in the short term.
- Phased testing/modification of the REMS. Test the components of the REMS and modify accordingly is the approach the IWG recommends.
- Phased development of the REMS.

The key components of the revised draft IWG REMS are:

- **Medication Guide:** Product specific medication guides.
- **Communication Plan:** Dear HCP letters explaining the REMS and specific risks.
- **Timetable for submission of the REMS:** The IWG said this needs further dialogue between IWG and FDA and will be somewhat dependent on the phased modification and development of REMS components.
- **Phased Testing/Modification of the REMS:** Current tools for patient education, based on feedback from previous FDA advisory committee meetings, are ineffective. There also are limits on storage in pharmacies, and they can be expensive to print as well as store.

Dr. Smith said that the IWG does not support any ETASUs, including mandatory training and recertification. Instead, the IWG is proposing a single, class-wide opioid Medication Guide. He added that the patient-prescriber agreement should be incorporated into the REMS and told the FDA, "Further guidance is needed in order to develop the PMIS (patient medication information sheet), which will be incorporated into the REMS."

To assure safe use of Medication guides, Dr. Smith said prescriber training/certification logistically needs to be designed to prevent prescriber opt out, and evidence of training should be linked to the DEA registration/renewal process, providing a single point of entry for all opioid prescribers. He said IWG favors pursuing new legislation to change the DEA's scope of responsibility. Finally, Dr. Smith stressed the importance of collaboration among the various governmental agencies, adding, "These activities will require time to accomplish, including an act of Congress. The IWG proposed that, parallel to these efforts, the voluntary training program be instituted."

Dr. Smith posed three questions to the FDA:

- Is the FDA amenable to a phased REMS approach?
- Is the FDA willing to work with IWG and stakeholder groups on improving medication guides, including development of a single class-wide opioid guide?
- Is the FDA amenable to a voluntary training program?

The FDA's Dr. Jenkins asked what role there might be for states and medical boards in the training, noting that this might avoid the need for a legislative solution for DEA involvement. Dr. Smith responded, "We did, and we felt that to approach a single entity such as the DEA would give us the best chance of success."

The FDA's Axelrad asked if the IWG got feedback about three separate pieces of paper for the patients: the patient-prescriber agreement, the medication guide, and the patient medication information sheet, "We heard feedback that one piece of paper was the best for the patients." A King Pharmaceuticals spokesperson said, "We decided that every opportunity we had to give a person the same information or like information would make it more understandable for that particular person." She said that 55% of patients with chronic disease have access to broadband internet.

The FDA's Dr. Douglas Throckmorton, deputy director of CDER, asked what the IWG envisions for the patient-prescriber agreement. Would it be a required document? Once the agreement is in place, would it somehow be captured and forwarded to the pharmacy in advance of the prescription? Dr. Smith responded, "We would encourage their use and take measures to assess how they are using it. We would not send them to the pharmacy." He said that physicians could choose or not choose to use the agreement.

Dr. Nicholson reiterated the IWG's "do no harm" concern, noting that the IWG group "cannot effectively or legally do anything that has serious negative consequences for patients in the form of decreased access, particularly for medically underserved patients." She said that the IWG heard "overwhelmingly" from stakeholders that they want no mandatory training related to a REMS.

Dr. Nicholson told the FDA that there are 209 Medication Guides, with 66 of these part of a REMS. Two of these are for products covered by this REMS, "The institution of this class-wide REMS would add 18 more medication guides to the list. Medication guides are not as effective as they could be…They are difficult to read and understand…Medication guides are not always provided to patients…So, in addition to the patient medication information sheet, our modified proposal includes the possibility of a single, class-wide opioid medication guide. This will take some time to do."

She said that the IWG proposal for DEA certification "would be the most sensible, most comprehensive way to make sure that prescribers have the information they need" and would "empower patients to protect themselves and their loved ones against improper use of these medications." However, she said the "IWG alone cannot tackle this."

Dr. Nicholson said the next steps toward a REMS should include:

- A phased approach to the class-wide REMS, with an initial REMS for all drugs within the class.
- Concurrent multiple work streams to evaluate potential add-ons to REMS suggestions. She said potential add-ons include development of appropriate, targeted metrics for positive and negative consequences of REMS, a class-wide medication guide, and exploration of DEA registration linked to opioid medication.
- Stakeholders driving the bus.

The FDA's Dr. Rappaport said, "We very clearly have heard from the FSMB (Federation of State Medical Boards) that they don't think the DEA registration process is the right way to go, and they don't think that the DEA should be involved at all, so I'm rather surprised that you didn't get the same feedback." Dr. Smith said that at the stakeholder meeting he did get that feedback. Dr. Nicholson added, "We will make a request to them to provide some clarifying comments."

Questions to the IWG from the FDA and Audience Members

Asked how the revised draft IWG proposal differs from earlier FDA RiskMAPs (risk minimization action plans), Dr. Nicholson said, "The IWG absolutely wants to drive the process of getting this REMS developed to the satisfaction of the FDA and the stakeholders…The proposed REMS where we are at today is not where we started a few weeks ago. What we are proposing with the initial draft is very similar to the only approved REMS in the class. We have a draft REMS and a supporting document. It does include specific metrics. Part of the issue is the bigger issue of non-patient impacts…It is challenging, but we intend to work that out and offer up some solutions."

How would the REMS differ from a RiskMAP? Dr. Nicholson said, "There are some specific deliverables on the REMS vs. the RiskMAP. On the level of energy around assuring that

there is an impact…and it is perhaps heightened because of the reporting requirements. We are going to make a commitment to make X percent of reading guides on comprehension."

Prescriber training

The FDA's Dr. Throckmorton asked about prescriber training and the DEA linkage proposal, adding, "There were several questions about your focus on the DEA. One question was about the perceived enforcement nature of the DEA and whether that would negatively impact the use of opiates. The second concern…related to the timelines and the uncertainty of the use of that registration system. It would require congressional action, things that take considerable amounts of time. People asked what you would do in the meantime."

Dr. Smith replied, "We proposed that we go ahead and develop a training program…Based on metrics from that – the education response to it as well as the update − we would keep that program voluntary at this point…We would be doing that in parallel from the start. A training program would not be required." A prescribers' sub-team member of the IWG said, "If we get to a point − special certification or training or a hybrid or both − when the doctor checks the box on the DEA attestation certification, that is part of the enforcement. If we make this very onerous, it is likely there will be some dropout, and I think we need to be very careful and thoughtful how we go about this…Probably the net benefit is that we would be the bottom of the funnel to ensure that everyone who has the legal right to prescribe those drugs would meet that requirement."

Asked about the role of state boards, Dr. Nicholson said, "There are 70 state boards, and it would be more work for them, and we heard that they would favor the DEA taking it on − voluntary education, working with state groups to make sure that the recipients of that training and education are achieved and partnership with doctor dispenser communities." Dr. Smith said, "To create such a system, the problem we heard is that you can't adjudicate it at the point of pharmacy unless you have a registry of qualified prescribers, and that would lead to doctors opting out. We have heard very clearly that that is not what that group wants…One reason we're interested in the voluntary training program is to see whether we can get 200,000 or 300,00 prescribers."

The FDA's Axelrad asked if a DEA system is used, how the IWG would develop the materials. Would the professional societies do that, she wanted to know. An IWG member said, "Industry knows the most about its products in terms of the individual products and safety issues. The FDA knows a lot about the products as a class. Working together…we can paint with a broad brush…We would envision the FDA and industry working together." Axelrad asked, "If Dr. Smith thought that 200,000-300,000 doctors being educated would be great, what happens to the other 700,000 or so? Would that be acceptable?" Dr. Smith said that he didn't mean that that would be acceptable.

Dr. Rappaport asked, "You heard from your stakeholders that they would opt out if there were a mandatory training program, but they would support a voluntary program? Did you get some feedback and can you hone in on what it was specifically? What were the factors that would make a prescriber opt out because it was mandatory? To me if they are going to opt out (because it is) mandatory, they will also opt out if it were voluntary." Dr. Nicholson said, "There was an example in Europe where physicians had to register to participate, and there was a stigma attached to being one of a few who prescribe opioids. We have not fully explored that and that is part I think of our homework. It is a critical question and the difference of voluntary and mandatory."

Dr. Jenkins asked, "What was the feedback (from stakeholders) about competency testing after they take this voluntary or required education? Was there going to be a test to show that they learned the information? Continuing medical education (CME) has goals stated, and there are tests administered. So what is your thinking about not only a training program but a demonstration that you learned what we wanted you to learn?" Dr. Smith said, "That was discussed and there were some in favor of some kind of competency tests and some felt the training would be sufficient. I don't think we have an IWG position on that (yet)."

Dr. Jenkins asked about what incentives there might be to encourage physicians to take the training if it were voluntary. He said there were some suggestions of involvement of the medical liability insurance carriers. Dr. Nicholson said, "We talked about exploring incentives. We don't have a list but medical liability is interesting and should certainly be explored. One of the things we need to test is the tolerance of the prescribing community for whatever systems we would put in place." Gary Buehler, RPh, the FDA's director of the Office of Generic Drugs (OGD), CDER, asked if the concern about a mandatory program was because physicians would react negatively to something being mandatory? Dr. Smith said that doctors "were worried about doctors opting out and the burden in rural areas. The dispensers were concerned about anything that would delay access to medication for patients. So the greatest concerns were that physicians would no longer participate and that the pharmacists would have patients who would have delays in getting medication." Axelrad asked, "Why would they opt out? Too burdensome, don't want the training, their name is on a list?" Dr. Nicholson replied, "Any of those reasons."

Phasing-in a REMS

Will the FDA support a phased-in REMS? The FDA's Axelrad said that the IWG proposal looks like the risk management plans in place even before FDAAA, "How long would this phasing be, and how long would it be before we see a meaningful change?" Dr. Nicholson said that the stakeholders rejected immediate implementation of some ideas, but she said that it would take a year to get the medication guides out and be ready to assess comprehension. Getting a class-wide

medication guide would be a very important step, she said, adding, "In a way, any REMS can be a phased-in REMS. You start with the least burdensome, and here we are only doing a balance. We all recognize that this is a very difficult thing, and we don't want to do more harm than good. But we also want to strike a balance between curbing the problems we've seen with the drugs and affecting people's access."

Axelrad responded, "We would want to see something sooner rather than later…The time frames seem pretty lengthy – a year to get the letters out?" Dr. Nicholson said that there would be two phases in the distribution of letters, "The first would be in a few months, and the second phase would be in a few years…But, again, I promise you that the IWG is committed to work as quickly and efficiently as we can to fulfill the requirements and make a difference."

The FDA's Dr. Jenkins said that the phased-in approach assumes that there will be a link between DEA certification and training, "What is your fallback if that doesn't happen in a timely manner? We can't control what Congress decides to do, and this would be a very controversial area…Many groups who told you that they would opt out would suggest to Congress that the legislation was costly and not necessary. How long would we wait…under your schema?" Dr. Nicholson responded, "We could make a commitment on what time might be reasonable to wait for that, and if something doesn't happen, that we would have a Plan B ready to go."

Dr. Jenkins asked if they had thought about how the FDA could incorporate a provision that if Congress doesn't modify the Controlled Substances Act in a reasonable time frame, the Agency would impose a new requirement on manufacturers, "It seems like putting eggs in a basket that you may never actually see. That's one of my concerns – the linkage to DEA. The system doesn't exist, and it requires legislation, and we know sometimes Congress can act very quickly, and sometimes things take a long time, and sometimes they just don't happen." An IWG spokesman said, "If we can get a lot of people signed up and using that…you may not have to tie it to registration…We are just thinking down the road if these things don't work."

Dr. Jenkins requested clarification, "Are you suggesting that DEA registration is a part of your plan or a fallback if your plan doesn't work?" The IWG spokesman said, "We can support it if they move on this rapidly. If it looks like it will take longer, if 3 years down the road we haven't seen any action, we just say that we don't need it." Dr. Nicholson added, "The DEA registration is not one of the commitments we would make as part of our REMS, but we are hopeful, and we are talking about it."

Mary Willy, PhD, from the FDA's Office of Surveillance and Epidemiology's Division of Risk Management questioned, "The assessment you looked at early on looked at people training voluntarily?" An IWG official said, "This would be certified training of prescribers. You have the American Chemistry Council (ACC), a nursing equivalent, and we would keep pretty close track of who was offering certified training consistent with the REMS and seek numbers from them."

Metrics

Dr. Willy commented on the several questions from the IWG to the FDA, "We have a metrics working group, and many of the questions you have are questions we will be addressing as we move forward. I was hoping for some detail from you about what are good data sources. You had a question about definitions, and we are working on that, but we'd like to hear from you on that, too."

The IWG's Dr. Schnoll said, "We are looking at precisely what are the specific metrics that will allow us to evaluate each of those areas and look into whether or not there are methods available to collect those data in a meaningful way."

Dr. Jenkins said, "There was a reference to observation – that the trends of misuse and abuse may be improving. I got emails from (FDA) staff asking what data you are referring to because we are unaware of any data like that. The National Survey of Drugs 2002-2008, those data are looking at prescription drugs specifically. There is a leveling off of the data. It's been pretty much flat over that time period and not specifically for some of the opioids, but for some of the other prescription drugs it has gone down. So, we are looking at that very carefully…When you look at these data, you have inclusion of both extended-release and immediate-release (IR) drugs, so it's hard to parse out what may be driving all of that. We need to look at these data sources very carefully in order to understand what is being measured."

Dr. Rappaport said that the National Survey data is patient-reported outcomes. It's very subjective and in many ways flawed. The Drug Abuse Warning Network (DAWN) data are actual medical data from emergency rooms, and that data are showing the numbers continuing to rise, so I am wondering what you think about that?" Dr. Schnoll said, "There have been some changes in the data collection for DAWN. It's gone from 22 metropolitan areas down to 12, and there are different weightings that are put on cases that come in to different areas, so the weighting that would be put into a major metropolitan area like Washington would be different from a hospital in a rural part of Kansas. Those weightings can influence what is published…so we are beginning to look at this more carefully."

Dr. Jenkins asked Dr. Schnoll to submit that information to the docket, adding that some of the discussion about postponing the docket was an opportunity to get more information in the public realm.

Patient education

The FDA's Deborah Miller, health programs coordinator for the Office of Special Health Issues (OSHI), Office of the Commissioner, asked about the proposal for a single class-wide medication guide, "What would you do with products that already have a medication guide? Would they then have two?" Dr. Smith said, "We heard from stake-holders that it's not the medication guide itself. There are many medication guides out there, and they are not written to a patient's perspective. The thought was that an indi-vidual company could come to an agreement with the FDA faster than all the companies. We are hearing the stake-holders want it to look completely different…It's our opinion that that will require some change as to what the FDA now considers as a medication guide."

Asked about the barriers to a single guide, Dr. Nicholson said, "You would have to find a mechanism for finding a product's specific safety information in with the other (information)…It might be easier to create those individual medication guides…We could not reconcile all those different medication guides. We think that we can get the PMIS (patient medication information sheet) out at the same time as the medication guides, but it would be two pieces of paper instead of one." An IWG member said that the doctor's office would give out the PMIS. Dr. Schnoll added, "We want to make sure that all the materials given to patients are carefully tested to make sure that they will be useful. We know that a lot of materials are not used and not well understood."

Dr. Jenkins said, "We've heard about compensating for the time it takes to educate patients. You're asking the prescriber to educate the patients and go over the sheets." An IWG member said that it was an option.

Dr. Jenkins noted that the IWG proposal for the companies to work with the FDA to create 18 medication guides, while fairly easy for the companies, would be a "logistical nightmare" for the short-staffed FDA reviewers.

Patient-Prescriber Agreements (PPAs)

An IWG member said that these agreements would create some consistency in the doctors' world, "In the event that a patient is not able to sign, there is also a spot for an agent and that is an important step."

Dr. Jenkins asked how likely the prescribers are to use the agreements in general practice, "If they are unwilling to be trained in how to use the products, what is their willingness to use this tool?" An IWG member said, "It is becoming more widespread...If it were involved in a REMS program…there would be a dramatic uptake in use."

Miller asked if periodic laboratory drug screening as part of a REMS is being considered. An IWG prescriber sub-team member said that risk stratification for certain patients is being discussed, "(It could encourage) practitioners to stratify risk based on known risk factors of an individual. Some have clear stratum…and regular drug testing might be part of that care. The agreement allows for the option, but we are still thinking about it."

Scope of the REMS

Noting that there has been a lot of interaction between IWG and stakeholders about the REMS, Dr. Rappaport asked:

1. Why was the abuse of opioids for non-medical purposes not addressed by the IWG? Dr. Nicholson responded, "We are very concerned about the non-medical use of these products. Our sphere of influence is largely with the patient and that chain of command…It is woven into all of our education (materials)."
2. Can you respond to the likely outcome of shifting abuse to short-acting opioids? Dr. Nicholson said that the IWG can't venture into the area of short-acting opioids because of antitrust laws.

Concluding Remarks

In closing, Dr. Nicholson said that she wanted to reiterate some of the questions the IWG submitted to the FDA. She asked for a timeline for a REMS, "What date is the FDA targeting for sending letters? How does the FDA plan to notify the IWG when a new company is placed under the REMS? We have had some companies approach us and ask to participate, but our charter only allows companies specifically designated by you to participate."

Dr. Jenkins said that he doesn't have all the answers, "but some of the logistics questions can be handled off-line regard-ing how to notify about new or departing members. We made clear that any products in this class − before we approve a final class REMS − will be under a temporary REMS…We are looking at dates for a public advisory meeting in the spring (2010). I can't be more definitive. We believe that a public advisory meeting to give FDA advice before we finalize our thinking on the REMS is important for us…We anticipate that we will be making public some information in advance of that advisory meeting that will lay out some of the FDA's thinking. That will be coming before the advisory meeting in plenty of time. This is a very complex program as we all have acknowl-edged, and we want to make sure that we have all the informa-tion. At the same time, we don't want to take forever. I can't give you a timeline for when the FDA would be ready to send the final letters to the companies outlining the components of the REMS because there are still a lot of unknowns. We could come up with a very good program and take it to the advisory committee, and we could get feedback to reconsider, so it's too uncertain for me to say…This meeting was very produc-tive, and it was interesting to hear some of the things you are working through. We are committed to continuing to move the process forward and the next public discussion is likely to be at that advisory committee meeting…Keep working, keep your nose to the grindstone."

FDA Post-Meeting Comments

At a news conference after the meeting, Dr. Jenkins said this meeting was another step in the pathway toward a REMS for this group of products, "We encouraged (the companies involved) to work together…(This) meeting was to allow them to share with us the thinking they've been going through and the feedback they heard from stakeholders but also to share with us their current thinking about what a proposal might look like. They had a proposal for a phased-in approach to developing a REMS, and we heard a lot of questions that they're seeking answers for…There were no definitive conclusions from the meeting, and we discussed the timeline that we are looking to conduct a public advisory committee meeting sometime in the spring."

Asked what he heard from the IWG about physician certification and training, Dr. Jenkins said, "We heard from them that they believe it would be an optimal solution if there were a linkage between the training and expectations and DEA registration for prescribing controlled substances in this class …Currently, physicians who prescribe those substances have to have a DEA registration, but there is no specific training required before you get that number, and the IWG proposed that there be a requirement that physicians or prescribers seeking DEA registration for Schedule II would be required to certify that they had received training on proper use of the medications…The (IWG) suggestion would be that, as part of the (DEA) registration, you (physicians) attest that you have taken a CME (continuing medical education) course that deals with the appropriate use of Schedule II narcotics. If it is a requirement of DEA registration, physicians could still opt out by not choosing to seek Schedule II prescribing privileges, but that would be a check itself."

Dr. Jenkins added that IWG is reluctant to build a completely separate system for hundreds of thousands of registered prescribers, "They are reluctant to build a parallel system for identifying who those trained prescribers would be so the pharmacist would know who the prescription should be written by…The IWG is reluctant to build a parallel system, given the fact that a system already exists."

Dr. Jenkins said the FDA has had discussions with the DEA, and its interpretation is that they don't have the authority to link registration with a certification of training. He said it would require new legislation for DEA to have the authority to require a physician attestation of completion of training, "In lieu of that, they (IWG) proposed that they would like to develop voluntary training programs that physicians would be encouraged to complete…but at this point it would be a voluntary program…to offer the training as a CME-type program but on a voluntary basis." Dr. Throckmorton added, "I believe as we heard from the IWG, that the DEA system would follow a period where there would be a more voluntary approach."

Asked how the FDA's stakeholders meetings differed from what the IWG told the panel, Dr. Jenkins said, "We've heard those same points raised in the various stakeholder meetings with regard to physician training. If the requirements are too burdensome, some physicians would choose not to be involved in the program and may opt out in prescribing the medications, and the concern would be that patients would have more limited access to doctors…The challenge we have to face is that we have to recognize that there are significant and serious ongoing safety concerns that we need to address. We heard the concerns and issues, and now our job is to find the solution that meets the twin goals of ensuring the safe use of these drugs while assuring access to appropriate patients." Dr. Throckmorton added, "While we've heard this perception that changes in the system might make people less likely to prescribe and make medications less available, in the discussion part we also heard how little data we have about what choices physicians make when confronted with systems like this, so we need a lot more information."

Asked why the FDA is focusing on the long-acting vs. short-acting opioids, Dr. Jenkins said, "We've chosen to focus our attention on sustained-release and long-acting opioids because that is an area where we have had a concern about the serious adverse events when the products are not used correctly… That's where we see a real signal of safety concerns…There are also safety concerns with the more immediate-release opioids, but the sustained-release opioids have unique properties that lead us to focus on them. ***One concern is whether the scope of our proposed opioid REMS is appropriate or whether the scope should be broadened and that's not a decision that we have reached yet***."

Asked if the FDA expected a little more from the IWG or if the Agency was disappointed with the IWG proposal, Axelrad said, "That's a difficult question to answer. I would say that I would have liked to have heard more specifics about what they were actually proposing. Because we did not hear in terms of specifics at the meeting, we will have to look at other ways to get information and input from them as to what the specifics are…We haven't talked about what we think the REMS should look like....We heard from them that they did not have a lot of time between their stakeholders hearing and (this meeting)…so they weren't given a huge amount of time."

The IWG proposed that in the interest of quickly getting information out to patients about these products, that they would develop a product-specific medication guide to each of the products, and they listed 18 unique products, not counting the generics that would need to have a product-specific medication guide. Dr. Jenkins said, "The IWG thought that would be the fastest way to get the guides to the patients. That would be instead of developing a class medication guide. I commented that while it might sound more efficient from a company perspective, we would then have to review 18 medication guides for 18 different products, so our review staff would have to look at the labeling for those individual products and work through the required format and content under our…regulations. We have a relatively small staff of experts who review the guides so having them face 18 is more of a logistical problem for us than having them make one class

medication guide…That said, there are product-specific issues that patients need to know about as well."

Asked what he would like to see in a REMS beyond what the IWG proposed – the patient medication guides, letters to HCPs, and voluntary training, Dr. Jenkins said, "That's the 65 million dollar question. We have to decide if prescriber education is going to be voluntary or mandatory and, if mandatory, you have to set up a system to collect a list of who has received the training because the pharmacists need to know who the list encompasses. Those are decisions that we still have to reach in terms of the final character of the REMS."

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