



Opening Remarks for Drug Safety and Risk Management and Dermatologic and Ophthalmic Advisory Committees Meeting

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Background

- Food and Drug Administration Amendments Act (FDAAA) of 2007
 - provides FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) if the Agency determines that a REMS is necessary to ensure the benefits of the drug outweigh the risk.

Elements of a REMS

- A REMS can include:
 - A Medication Guide or patient package insert
 - A Communication Plan to healthcare providers
 - Elements to assure safe use (ETASU)
 - An implementation system
 - Timetable for submission of assessments

Elements to Assure Safe Use

- The following elements can be included:
 - Healthcare providers who prescribe the drug have particular training or experience, or are specially certified
 - Pharmacies, practitioner, or health care setting that dispense the drug are specially certified
 - The drug is to be dispensed to patients only in certain health care settings, such as hospitals
 - The drug is to be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
 - Each patient using the drug is to be subject to certain monitoring
 - Each patient using the drug is to be enrolled in a registry

Additional FDAAA Requirement

- Requires the Agency, at least annually,
 - to bring at least one drug with a REMS with elements to assure safe use (ETASU) to the Drug Safety and Risk Management Advisory Committee (DSaRM)
 - solicit views of DSaRM on whether the elements
 - Assure safe use of the drug
 - Are not unduly burdensome on patient access to the drug
 - To the extent practicable, minimize the burden on the healthcare delivery system

Today's Meeting

- The morning meeting will focus on the evaluation of one drug that has a REMS with ETASU, the isotretinoin REMS, called iPLEDGE
- The afternoon meeting will be a general discussion of how REMS programs may be implemented to minimize the negative effects on patient access to drugs covered by REMS and to decrease the burdens of REMS on the healthcare system
 - The afternoon meeting will not include any drug-specific information

Conclusion

- The committee members will be asked to consider and discuss several points
- This meeting represents the first opportunity
 - for FDA to discuss an assessment of a REMS with ETASU
 - to discuss important REMS-related issues
- We look forward to the discussion



History of Pregnancy Exposure Risk Management for Isotretinoin

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Lead Medical Officer

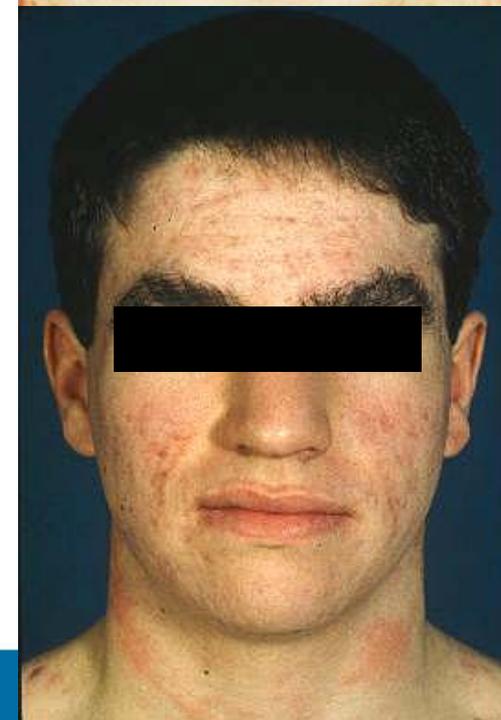
Division of Dermatology and Dental Products

Office of New Drugs, ODE III

Center for Drug Evaluation and Research

Isotretinoin indication

- Severe recalcitrant nodular acne
- Sole drug approved
- Complete and prolonged disease remission in many patients after single 15-20 week course of therapy
- Off-label use includes
 - Scarring non-nodular acne
 - Neuroblastoma
 - Other cancers



Regulatory history

- Accutane approved 1982
- Generic products
 - Amnesteem 11/2002
 - Sotret 12/2002
 - Claravis 4/2003
- Accutane withdrawn 2010
 - Not for safety or efficacy

Teratogen

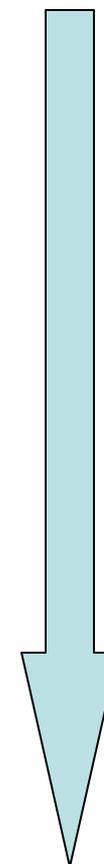
- Increased risk of spontaneous abortion and premature birth
- Major malformations: craniofacial, cardiac, thymus, CNS, functional
- High frequency of effect in exposed pregnancies
- No known safe dose/exposure window during gestation
- Long history of risk management

Risk management

- Risk assessment + risk minimization
- Four step process
 - Assessment of benefit-risk balance
 - Development and implementation of tools to minimize risks while preserving benefits
 - Evaluation of tool effectiveness and reassessment of benefit-risk balance
 - Adjustment of tools to further enhance benefit-risk balance

Risk minimization tool kit

- Routine measures
 - Rx status
 - Professional labeling
- Targeted education and outreach
 - Dear Health Care Provider letters
 - Medication Guides
- Reminder systems
 - Consent forms
 - Limitations on amounts dispensed/refills
 - Specialized product packaging
 - Prescription stickers
- Performance-linked access systems
 - Dispensing only with documentation of safe-use conditions



Four eras of isotretinoin risk management

1. 1982 – 1988: early marketing
2. 1988 – 2002: Accutane Pregnancy Prevention Program
3. 2002 – 2005: sticker-based programs
4. 2006 – present: iPLEDGE

Early marketing: 1982-1988

- Nonclinical signal for teratogenesis
 - Contraindications, Warnings, Precautions
 - Pregnancy category X
- Human data accrued (fetal exposure)
 - Labeling: Boxed warning 1984
 - Dear Doctor/Dear Pharmacist letters
 - Red warning stickers for pharmacist to apply to dispensed prescriptions
- Pregnancy exposures continued

Pregnancy Prevention Program: 1988-2002

- Sponsor proposed Pregnancy Prevention Program (PPP)
- PPP presented to the advisory committee in 1988

PPP Elements 1988-2002

- Revised labeling
- Targeted education and outreach tools
 - Dear Doctor letters
 - Patient brochures
- Reminder tools
 - Patient informed consent forms
 - Blister pack w/“avoid pregnancy” icon
 - Limitation of amount dispensed
- Assessment instruments: patient and prescriber surveys

PPP Assessment 1988-2002

- Substantial non-compliance with critical elements of PPP
- Low survey participation
- Pregnancy exposures continued
- Advisory committee convened in 2000

2000 Advisory Committee goals for isotretinoin risk management

- No woman begin isotretinoin therapy if she is pregnant
- No pregnancies occur while a woman is taking isotretinoin

Advisory Committee recommendations in 2000

- Augmentation of patient education
- Registration of all patients
- Registration of prescribers
- Implementation of pregnancy registry
- Linkage of prescription to adequate pregnancy testing

Sticker programs: 2002-2005

- Based on need for fetal exposure risk management, AC recommendations, and extensive discussions and negotiations between HLR and FDA
- Approved for innovator in October 2001
 - Accutane S.M.A.R.T.
- Generics' plans included essential elements
 - Amnesteem: S.P.I.R.I.T. November 2002
 - Sotret: I.M.P.A.R.T. December 2002
 - Claravis: A.L.E.R.T. April 2003

Sticker program tools

- Continued the content and tools of PPP
- Revised labeling
 - 2nd pregnancy test within first 5 days of menses
- Targeted education and outreach tool
 - Medication Guide dispensed with each prescription
- Reminder tools
 - Prescriber attestation
 - Yellow qualification sticker on prescription

Assessment of sticker program

- Hoffman-La Roche and FDA agreed to assess impact of sticker program after one year: Prescription Compliance Survey and Patient Survey
- HLR proposed metrics:
 - Increase patient survey enrollment to 60%
 - Demonstrate $\geq 90\%$ Accutane Rx's had qualification sticker
- 2004: HLR, FDA, and Advisory Committee agreed that sticker program did not meet objectives

Sticker program impact

- No decline in number of exposed pregnancies in survey cohort
- Low participation in voluntary survey
- Sticker use an imperfect surrogate for pregnancy testing

February 2004 Advisory Committee DODAC/DSaRM

Recommended that isotretinoin risk management be strengthened and consolidated

- Registration of all patients, male and female
- Registration of all prescribers
- Registration of all pharmacies
- Tightly link pregnancy testing to dispensing of drug
- Establish a pregnancy registry for root-cause analysis

iPLEDGE: 2006 - present

- Technology-based pregnancy risk management program to prevent fetal exposure to isotretinoin
- Restricted distribution
 - Only registered wholesalers/distributors ship isotretinoin
 - Only registered and activated pharmacies receive/dispense isotretinoin
 - Only registered and activated prescribers prescribe isotretinoin
- Performance-linked access system
 - Registered and qualified patients receive isotretinoin

iPLEDGE: 2006 - present

- Approved August 12, 2005
- Stakeholder registration (wholesalers and pharmacies) began in September 2005
- Patient enrollment opened December 30, 2005
- Transition completed March 1, 2006

New Elements

- Single, consolidated program for innovator and generic firms
- Documentation monthly counseling for all patients
- Documentation monthly CLIA-certified laboratory pregnancy testing for FCBP
- Demonstration of comprehension by FCBPs: answering monthly questions
- Pregnancy registry for root cause analysis

Unique Aspects of iPLEDGE

- Single consolidated program for both innovator and generic products
- First performance-linked access system for widely prescribed drug
- Multi-source marketplace

Advisory Committee discussions

1988

2000

2004

2007

2011



	1982–1988 Early	1988–2002 PPP	2002–2006 Sticker programs	2006–present iPLEDGE
Routine Measures				
Rx status	X	X	X	X
Professional labeling	X	X	X	X
Targeted Education & Outreach				
HCP letters	X	X	X	X
Patient labeling	X	X	X	X
Medication Guide			X	X
Reminder Systems				
Consent forms		X	X	X
Limit amt dispensed		X	X	X
Specialized packaging		X	X	X
Prescription stickers			X	
Performance-linked access systems				
Stakeholder registration				X
Rx linked to safe-use conditions				X

iPLEDGE: Effects on Burden and Access

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Objectives for this presentation

- Discuss burden of iPLEDGE
 - Define burden in the context of REMS with elements to assure safe use*
 - Discuss challenges with measuring iPLEDGE-related burden
- Discuss patient access to therapy in iPLEDGE
 - Define patient access in the context of REMS
 - Present a framework for evaluating access under REMS
 - Review the analysis of iPLEDGE effects on patient access
 - Illustrate challenges with measuring iPLEDGE-related access

In this presentation, I will use the acronym REMS to refer to REMS with elements to assure safe use (ETASU)

Burden is inherent in risk mitigation

- Risk management by its nature imposes at least some level of burden on the healthcare delivery system
- REMS, including iPLEDGE, emphasize safe use practices for the drug in question, e.g.
 - Verifying that a patient about to receive isotretinoin is not pregnant
 - Counseling about the nature of the risk
 - Counseling what the patient needs to do to minimize risk
- REMS may also introduce new risk mitigation measures, e.g., pharmacists verify that safe use conditions are met
- Administrative checks support these risk mitigation efforts
 - Documenting and verifying that safe use practices are followed

Burden of REMS: What are we attempting to measure?

- FDAAA places emphasis on **minimizing burden**

“evaluate (...) whether the elements [to assure safe use], (...) to the extent practicable, minimize the burden on the health care delivery system”

- Describing burden alone falls short of FDAAA’s evaluation goal
- Measuring whether burden could further be lowered requires identification of a process that is more efficient but does not compromise risk management goals

Is iPLEDGE overly burdensome?

- Burden-lowering enhancements have been implemented
- Not clear how an assessment can be done to identify the extent to which iPLEDGE currently minimizes the burden
 - Assessing this requires identifying a more efficient risk management mechanism/process, which does not compromise risk management goals
- Another way to look at whether iPLEDGE is overly burdensome is to consider its impact on patient access
 - Burden of REMS processes may translate into providers' unwillingness to prescribe a clinically appropriate therapy

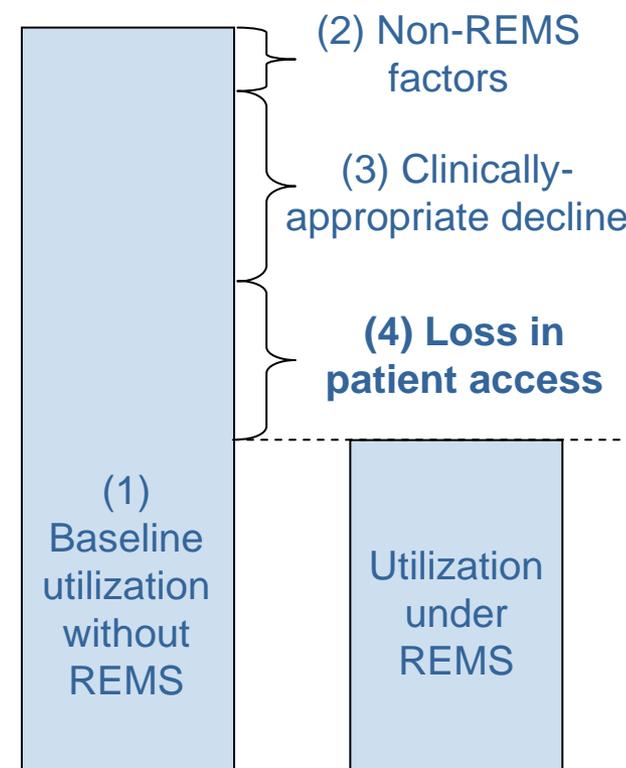
Impact on patient access: What are we attempting to measure?

- FDAAA requires an evaluation of whether the REMS are unduly burdensome on patient access to the drug
- Common definition of access-to-care* is the ability of a person to receive health care services, which is a function of:
 - Availability of personnel and supplies and
 - Ability to pay for those services
- In the context of REMS, patient access is the ability of a person to receive a drug under clinically appropriate conditions
 - Some REMS are designed to limit certain uses, e.g., use of a teratogen in pregnant women
 - REMS are generally designed to provide information about risks, which may lead to lower prescribing

**Source: McGraw-Hill Concise Dictionary of Modern Medicine*

Framework for analyzing patient access in the context of REMS

- Assessing impact on access requires:
 - (1) Defining an appropriate baseline
 - (2) Accounting for non-REMS factors
 - (3) Accounting for clinically-appropriate decline by:
 - (a) Isolating targeted inappropriate use
 - (b) Accounting for effects of education and/or new information
- Remaining difference in utilization can be used as surrogate for loss in patient access
- Goal of analysis is to estimate magnitude of components 2-4 above in the short term and long term



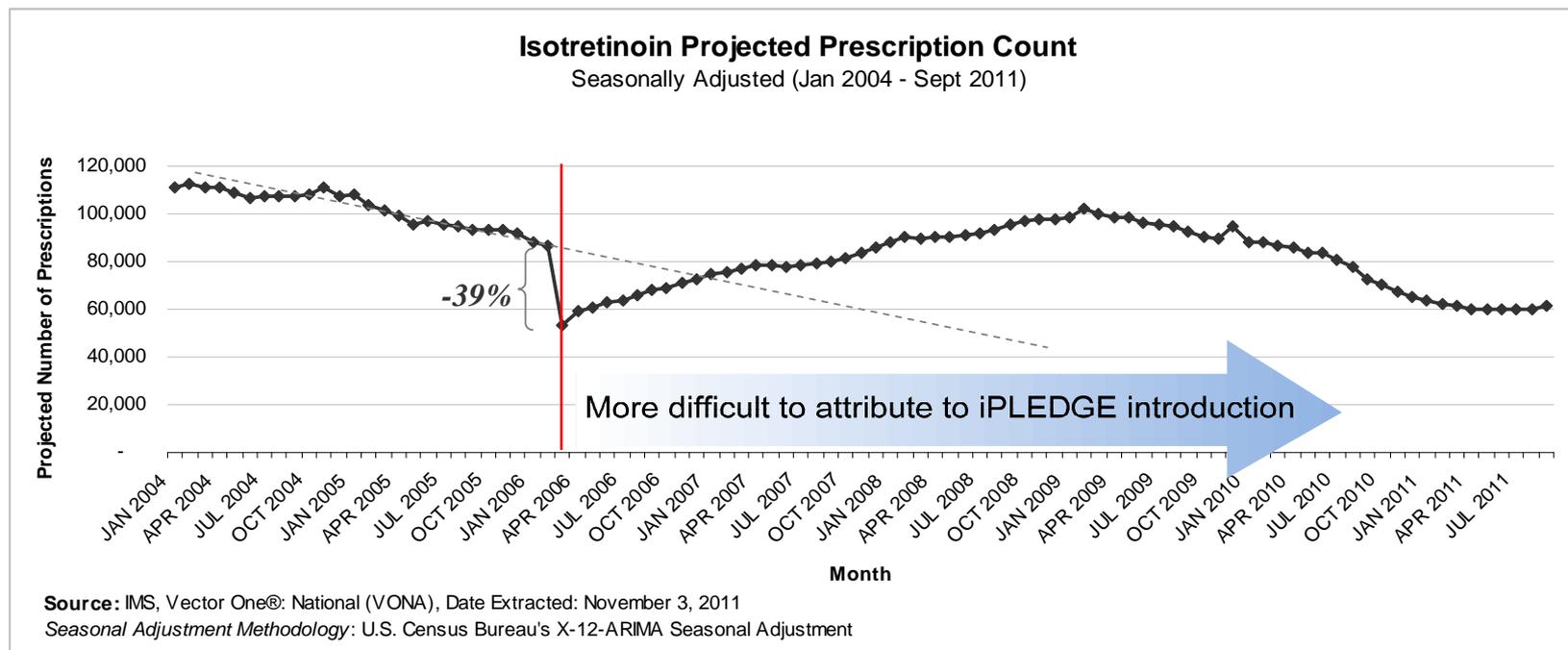
Analysis of patient access: Methods

- Our analysis of access under iPLEDGE
 - Isolate non-REMS effects
 - Account for clinically-appropriate decrease in utilization
 - Focus on introduction of iPLEDGE
 - Study various metrics around patient utilization and provider participation
- We use several sources of data
 - Projected national Rx claims data (IMS, Vector One®: National VONA)
 - De-identified longitudinal sample of patients (Wolters Kluwer® CPA)
- We adjust for seasonality
 - Isotretinoin prescriptions exhibit strong seasonal patterns
 - Use Census Bureau ARIMA-12 seasonal adjustment software

(1) Establish baseline and (2) Isolate non-iPLEDGE factors

- Baseline: pre-iPLEDGE utilization
 - This baseline allows us to make inferences about iPLEDGE introduction, but inferences about today are not possible
 - Understanding the impact at introduction, including any short-term disruption, is important from perspective of future REMS
- Introduction of iPLEDGE did not coincide with other events that may affect utilization:
 - No new competing therapies were introduced
 - No discernable price or copayment changes took place
 - Media coverage was related to iPLEDGE
 - Time series were adjusted for seasonality

Introduction of iPLEDGE resulted in a 39% utilization drop with recovery in 10 months

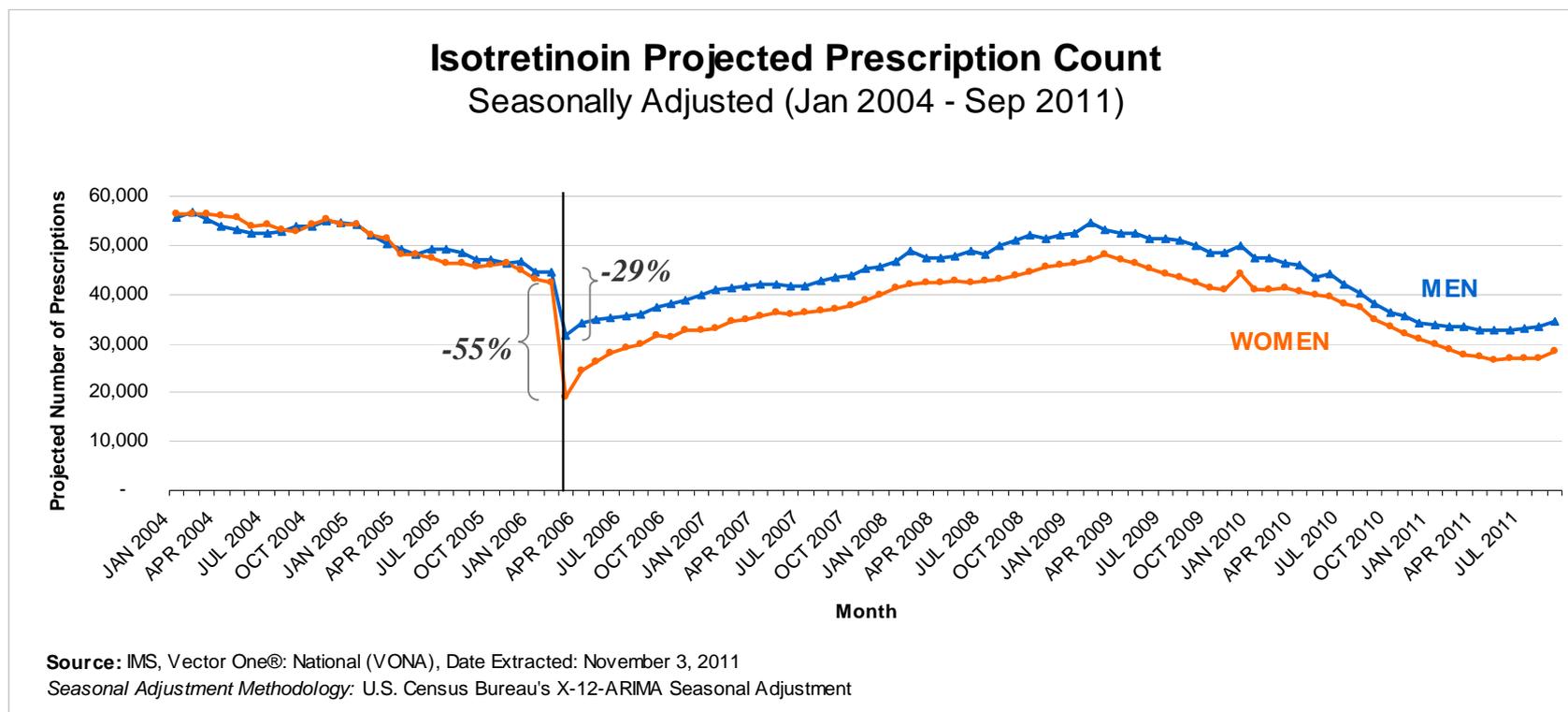


With no obvious utilization-lowering events unrelated to iPLEDGE, the 39% drop could be attributed to iPLEDGE becoming mandatory.

(3) Account for clinically-appropriate decrease in utilization

- iPLEDGE intends to prevent use by:
 - Pregnant women
 - Sexually active women not using appropriate contraception
- New information about risk may change a patient's or provider's assessment about the benefit-risk balance of isotretinoin
 - Part of iPLEDGE is an acknowledgement of risks and education about ways to mitigate the risk
 - Such clinically-appropriate reassessment may lead to a decrease in utilization
- Because of the focus on pregnancies, it is useful to consider iPLEDGE impact on utilization by gender

Introduction of iPLEDGE had a differential impact on use by men and women



Women face higher program requirements than men and the decline likely reflects that fact. But what about effect on clinically-appropriate use?

Short-term drop in utilization by men is most likely attributable to loss in access

- Introduction of iPLEDGE lead to a 29% decrease in utilization, which then returns to trend in 7-8 months
- iPLEDGE focuses on pregnancies so utilization by men should not have changed for clinical reasons
- The 29% initial drop could be interpreted as a decrease in patient access because
 - No identifiable factors unrelated to iPLEDGE took place in March'06
 - No clinically-appropriate decrease in prescribing to men is expected
- The return to pre-iPLEDGE utilization levels suggests that, on a broad population level, there may not have been an access problem for men past month 8

Changes in clinically-appropriate use and access are confounded for women

- Women's utilization initially decreased by 55% and returned to pre-iPLEDGE trend within a year
- Women face higher requirements than men and the decline likely reflects that. But what about clinically-appropriate use?
- iPLEDGE enhanced but did not introduce risk-mitigation efforts that may affect clinically-appropriate use:
 - Pregnancy prevention was the focus of education in prior program
 - Same uses were targeted by the prior program
- Nonetheless, disentangling the new requirements from potential changes in clinically-appropriate use is difficult

What are the possible explanations for the apparent initial access disruption?

- Technical impediments during implementation
 - Less than 10% of known prescribers registered their patients with iPLEDGE during phase-in
 - Calls initially exceeded call center capacity
- iPledge-related decrease in patient demand
 - Some patients may perceive the requirements as overly burdensome
- iPledge-related decrease in prescriber participation

Physician participation is a key component of patient access to therapy

- Decrease in patient access may occur when burden on providers translates into their unwillingness to prescribe a clinically appropriate therapy
- We studied the impact of iPLEDGE introduction on the number of prescribing physicians
 - Used a large longitudinal sample of isotretinoin patients from Wolters Kluwer® CPA
 - Identified the number of active prescribers in a given month by specialty and location
 - Adjusted time series for seasonality us Census ARIMA-12
 - Assessed the change in the number of prescribers at the time iPLEDGE became mandatory

Effect on patient access was in part driven by lower physician participation

- Effect of iPLEDGE differed by specialty rather than location
 - The number of prescribing dermatologists initially declined by a lower percentage than the number of non-dermatologists (15% dermatologists vs. 36% other)
 - This may reflect the fact that dermatologists are heavier prescribers
 - The initial percentage decrease following full iPLEDGE roll-out was similar by location (22% in rural vs. 20% in urban)
- In contrast to utilization, the number of active prescribers appears to have dropped permanently after iPLEDGE
 - Instead, the average number of patients per active prescriber rose

Takeaways about iPLEDGE impact on burden and patient access

- Risk management imposes burdens; goal is to minimize burden
- Assessment whether PLEDGE minimizes burden requires identifying a risk management process that is more efficient but does not compromise risk management goals
- Evidence that iPLEDGE initially adversely affected patient access but that it recovered within a year
 - Impact: combination of stakeholder response and implementation
- Methodology but not iPLEDGE experience extrapolates
 - Different REMS have different requirements
 - Same requirement may be implemented differently
 - Severity of condition and availability of treatment options may affect patients' and providers' willingness to embrace burden

FDA Perspective iPLEDGE Assessments

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REMS assessments

- A *Risk Evaluation and Mitigation Strategy* is dynamic throughout the life cycle of its product
- Assessments are required periodically
- In each assessment review, we ask:
 - Is the REMS meeting the risk mitigation goal?
 - Is the REMS necessary to ensure the benefits outweigh the risks?

Is iPLEDGE...

- Preventing fetal exposure to isotretinoin?
- Necessary for prevention of fetal exposure to isotretinoin?

Is iPLEDGE preventing isotretinoin fetal exposure?

- The number of fetal exposures to isotretinoin (pregnancy rate) is an obvious direct metric to assess whether iPLEDGE is meeting this goal
- This metric presents two problems

To use fetal exposures as the metric for iPLEDGE 'success' we must...

- Pre-define 'how many exposed fetuses are too many?'
 - The aspirational goal is that there be no fetal exposures to isotretinoin at all
 - Problem: all complex factors that contribute to unplanned pregnancy cannot be eliminated
- Know the number of isotretinoin exposed pregnancies
 - Problem: complete ascertainment is unlikely due to lost-to follow up and under-reporting

Why is the fetal exposure number unknown?

- Severe nodular acne is a serious medical problem, but it is not life-threatening
- Patients who stop isotretinoin on discovering pregnancy have no medical need to return to the prescriber
 - lost to follow-up
- Stakeholders with privacy or compliance action concerns
 - under-reporting

Clinically meaningful metric alternative

- iPLEDGE processes are designed to prevent fetal exposure by:
 - eliminating *knowledge* deficits that can contribute to fetal exposure
 - eliminating *clinical practices* that can contribute to fetal exposure
- Use *knowledge* and *clinical practice* metrics to assess iPLEDGE

The question
‘how-many-fetal exposures-are-too many?’
then becomes answerable



Any that could be prevented by
knowledge and best *clinical practices*

Patients

- iPLEDGE data indicate that women across age groups understand the risk and the need to prevent pregnancy
- As shown by the pregnancy root cause analysis, consistent correct use of 2 forms of birth control is the challenge

Healthcare Providers

- iPLEDGE data indicate that most HCPs are performing clinical practices aimed at fetal exposure prevention
- Most identified problems are knowledge/practice errors amenable to iPLEDGE re-training protocols
- Prescribers and pharmacies found to be intentionally bypassing iPLEDGE requirements that they agreed to follow are subject to iPLEDGE deactivation

Most frequent serious HCP problem areas

- *Pharmacists*: dispensing without a risk management authorization (RMA#)
 - Why serious? The RMA# is the key to the ‘closed loop’ system; it signifies that all iPLEDGE requirements have been met for the patient’s assigned risk category
- *Prescribers*: failure to correctly identify females of child-bearing potential
 - Why serious? Misclassification as FNCP allows iPLEDGE to generate a RMA# without completion of requirements aimed at preventing/minimizing fetal exposure

RMA# importance

- Ensures that prescribers cannot treat with isotretinoin if unaware of iPLEDGE or choose not to enroll – they can write prescriptions, but the drug won't be dispensed
- Does not ensure patient won't become pregnant during 30-day supply, but does ensure to practicable extent that she is not already pregnant and understands risk/prevention
- iPLEDGE's 30-day supply limit, coupled with monthly pregnancy testing prior to the next RMA, may limit fetal exposure duration and time between conception and counseling

Because the RMA# is key to iPLEDGE integrity...

- All patients, regardless of risk category, need to be enrolled and have a RMA# for each dispensing
- The pharmacy then need verify only that the RMA# has been generated by iPLEDGE

By dispensing only with a RMA#

the pharmacist is the barrier between a potent teratogen and a pregnant and/or inadequately informed patient standing at the pharmacy's counter

Strategies to address identified problems

- Risk category classification errors

new web 'wizard' will auto-assign based on approved labeling criteria for non-child bearing potential

- Dispensing without RMA#

technology innovations are needed to integrate pharmacy systems with iPLEDGE's RMA#



The afternoon session will address healthcare system integration in the larger context of REMS

FDA's perspective on iPLEDGE assessment

- iPLEDGE is ensuring delivery of needed knowledge and clinical practices for the majority of patients
- iPLEDGE does affect access and burden, but clinical practice burden is inherent to use of a potent teratogen
- No currently envisioned program can eliminate all fetal exposures
- This reality should not discourage robust efforts to achieve that goal, or justify denial of uniquely efficacious therapy

- iPLEDGE gives HCPs a powerful web-based tool to optimize the probability that all patients, under all healthcare delivery systems, benefit from systematized execution of best practices codified in isotretinoin's labeling

- Pending development of more advanced strategies for systematically managing use of potent teratogens, programs such as iPLEDGE are state-of-the art
- Programs such as iPLEDGE are required to ensure continued availability of needed drugs for eligible patients while minimizing the risk of fetal harm