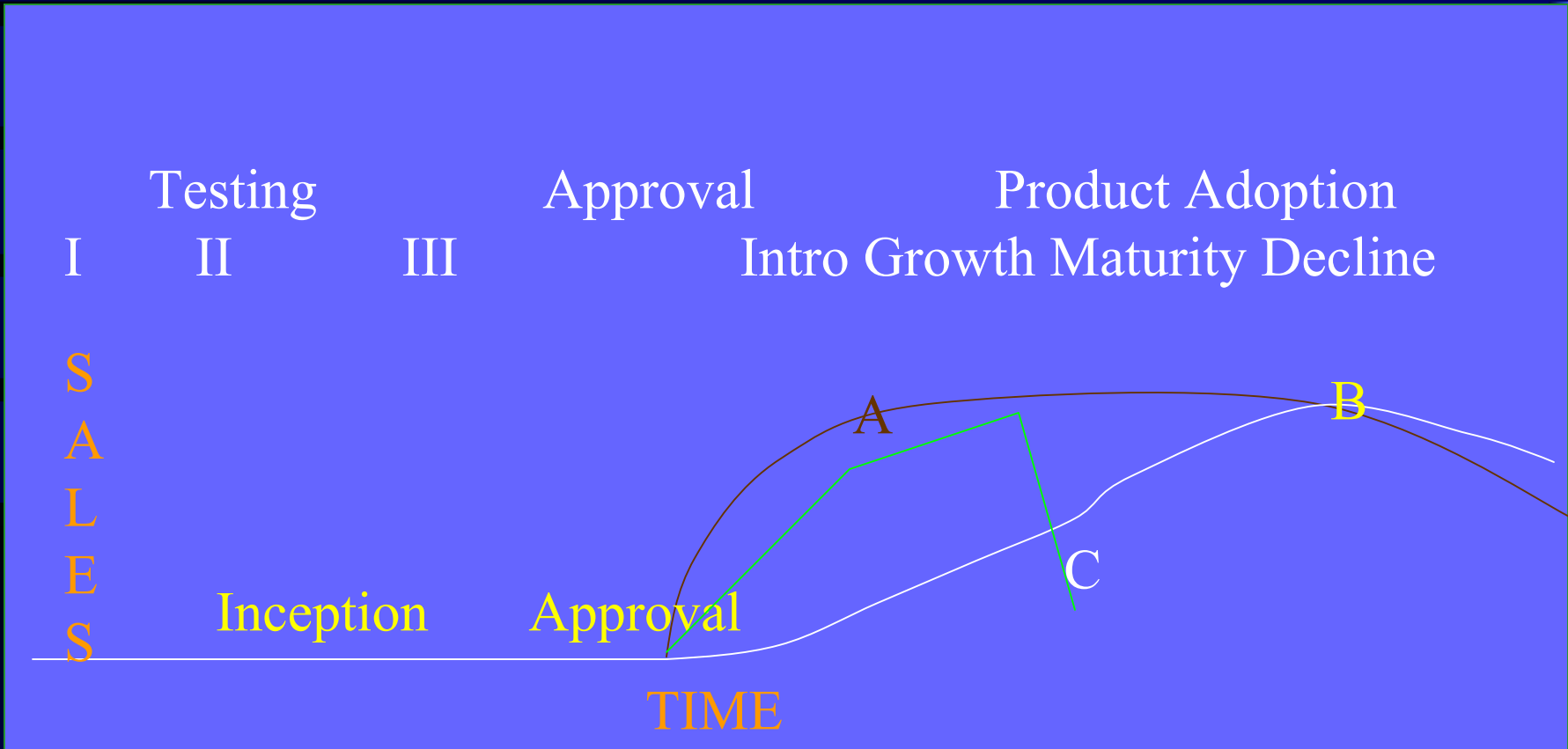


Developing a RiskMAP

Louis A. Morris, Ph.D.
FDA Regulatory Symposium
August 25, 2005



Challenge



What can we do in Phase I-III to assure A and avoid B and C?

Significant Withdrawals

• Seldane™ (terfenadine)	2/98
• Posicor™ (mibefradil)	6/98
• Duract™ (bromphenac)	6/98
• Hismanal™ (astemizole)	6/99
• Roxar™ (grepafloxacin)	11/99
• Propulsid™ (cisapride)	3/00
• Rezulin™ (troglitazone)	3/00
• Lotronex™ (alosetron HCl)*	8/00
• Raplon™ (rapcuronium)	3/01
• Baycol™ (cerivaxtatin)	8/01
• Vioxx™ (rofecoxib)	9/04
• Tysabri™ (natalizumab)**	2/05

* Reintroduced, ** Marketing temporarily halted

And in Recent Months

- Asthma Drugs Okayed to stay on market 7/05
- Palladone withdrawn 7/05
- ED Drug labeling (blindness: “we do not know if drugs” cause condition) 7/05
- Antidepressants (black box, suicidality) 6/05
- Duragesic black box added 6/05
- Natrecor (heart-failure drug) restricted to “acutely sick hospital patients” 6/05
- Iressa sales restricted to those who already take it and are benefiting 6/05
- ADHD Drug labeling (add: suicidal thoughts and hallucinations) 6/05
- NSAIDS (labeling, withdrawal of Bextra) 4/05

Objectives

- The New Era of Risk Management
 - FDA and Product Liability
- FDA Draft Guidance: RiskMAP
 - When will a RiskMAP be needed?
 - Selected drugs
 - What will be required for a RiskMAP?
 - How do I design a RiskMAP for my drug?
- Conclusions

FDA's Refined Concepts

- **Risk Management:** *“The overall and continuing process of minimizing risks throughout a product’s lifecycle to optimize its benefit/risk balance.”*
- Developing Interventions to prevent harm:
**Risk Minimization Action Plan
(RiskMAP)**

RiskMAP

- A strategic safety program
 - designed to minimize known product risks while preserving its benefits.
 - One or more safety goals and related objectives
 - Uses one or more interventions or “tools”
 - extend beyond the package insert and routine post marketing surveillance.
- Guidance describes:
 - conditions stimulating the need for a RiskMAP,
 - the selection of tools,
 - the format for RiskMAPs, and
 - the evaluation processes necessary to develop and to monitor the success of a risk minimization plan.

When is a RiskMAP Needed?

- FDA
 - the nature of risks verses benefits
 - risk tolerance issues such as population affected, alternative therapy available and reversibility of adverse events
 - preventability of the adverse event, and
 - probability of benefit or success of the risk minimization interventions
- Likely Candidates
 - Drugs that have serious or life threatening contraindications, warnings, precautions or adverse effects
 - When patient/professional behaviors can mitigate risks
 - such as pregnancy prevention, blood tests, overdose/misuse avoidance, awareness and action related to specific safety signals
 - When people other than the patient may be at risk
 - Such as, a child may use the product inadvertently
 - Schedule II drugs
 - Singled out by FDA, with concerns for misuse, abuse, addiction, diversion and overdose as likely candidates for a RiskMAP.

Look for Benchmarks, Narrow R/B Tolerances, Preventability, Signals

Examples of Drugs with RM Distribution Controls

- Accutane (isotretinoin) - severe recalcitrant nodular acne
- Actiq (fentanyl citrate) - severe cancer pain
- Clozaril (clozapine) - severe schizophrenia
- Lotronex (alosetron hydrochloride) - severe irritable bowel syndrome in women
- Mifiprex (mifepristone or RU-486) - termination of early intrauterine pregnancy
- Thalomid (thalidomide) - erythema nodosum leprosum
- Tikosyn (dofetilide) - maintenance of normal sinus rhythm
- Tracleer (bosentan) - severe pulmonary arterial hypertension
- Trovan (trovafloxacin mesylate or alatrofloxacin mesylate injection) - severe, life-threatening infections
- Xyrem (sodium oxybate) - narcolepsy

However, many drugs have educational interventions to minimize risks – what is the level of RM needed?

Practical Guide

- Who should not take “Drug”?
 - Absolute Contraindications, lab test values, pregnancy status, etc.
 - How should I take “Drug”?
 - Timing, delivery system, unique condition
 - What should I avoid while taking “Drug”?
 - Other meds, foods, activities
 - What are the possible or reasonably likely side effects?
 - Unavoidable, rare but serious
- Contraindication
- Usage
Directions
- Avoidance
Behavior
- Consent

Four Medication Guide Questions

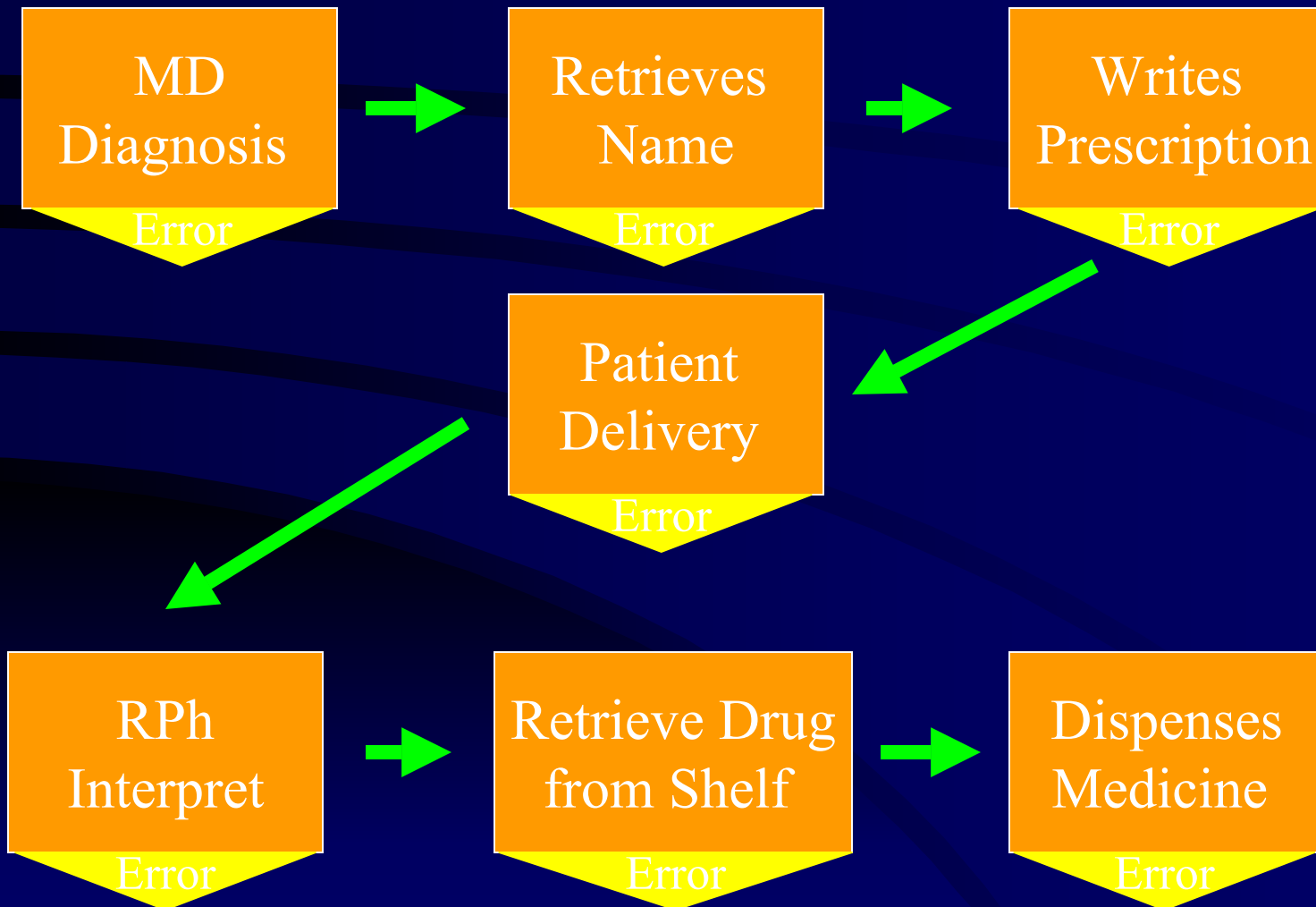
Designing a RiskMAP (1)

- Must clearly specify risk to be managed
 - Use PI (or target profile) to select and specify problems to be addressed
 - Organize and focus on problems needing RiskMAP
- Understand the “System”
 - Processes underlying drug prescribing, distribution and use
 - Use Root Cause or FMEA analysis to specify sources of system failures

Correctly “framing the problem” points to the best solution

System Analysis

Medication Dispensing



Failure Mode and Effects Analysis

- Develop System Steps (or subsystem)
 - Sources of Failure for each step
 - Probability
 - **Severity**
 - Likelihood Of Detection
 - Develop index by multiplication

Set Goals and Objectives

- Plan must specify
 - overall goals of the RiskMAP
 - the desired endpoints for safe product use.
- The objectives for each goal
 - must be specific and measurable.
 - specify the behaviors and processes necessary for the stated goals to be achieved.
 - For example, if our goal is to prevent pregnancy, then an objective may be that all women must have a negative pregnancy test performed within seven days of initiating therapy.

Designing a RiskMAP (2)

- Develop a behaviorally predictive model
 - the set of beliefs underlying behavioral intentions,
 - the motivations that support or stand in the way of exhibiting desired behavior and
 - the environmental conditions that facilitate or place barriers to compliance.

What do you want people to do?

Behavioral Models

- Attitude Change
 - Understanding Beliefs and Persuasion
- Improving Involvement (personal relevance) or Competency (self-efficacy)
- Decision making (mental models)
 - Think and act like experts
- Field Theory (barriers and facilitators)
- Stages of Change or Precaution Adoption
- Emotional Models (fear appeals or positive affect)

Choose the Model that best fits the problem

Designing a RiskMAP (3)

- Developing Interventions
 - Selecting Tools
 - FDA three classes are descriptive but not predictive
 - Suggest two class categorization
 - Informational Tools
 - Use Communication Model to select tools
 - Distribution Controls
 - Additional classes of tools available
 - Economic Controls (incentives for compliance)'
 - Product Modifications (reformulations, system delivery)
 - Combinations and systems improvements

Personal view: Tools fit the 4 Ps of Marketing

Tools: FDA Categorization

- “Targeted education or outreach.”
 - health care professionals (e.g., letters; training programs; letters to the editor).
 - promotional techniques to publicize risk management (e.g., advertisements and sales representatives’ distribution of information).
 - consumers and patients (e.g., Medication Guides and patient package inserts, limiting sampling or direct-to-consumer advertising)
- “Reminder systems.”
 - training or certification programs, physician attestation, patient agreements), specialized packaging limiting the amount of medication dispensed
- “Performance-Linked Access Systems.”
 - acknowledgment, certification, enrollment, or records
 - Limiting prescribing to certified health care practitioners,
 - limiting dispensing to certified pharmacies or practitioners
 - Limiting access to patients with evidence of fulfilling certain conditions (e.g., negative laboratory test results).

Not particularly helpful for planning...Exanta review, FDA pointed to lack of Reminder and Performance Systems

Tools Selection (FDA)

- Necessary And Sufficient for Influencing Behavior
- FDA: Selecting Tools
 - Input from stakeholders
 - Consistency with existing tools
 - Documented evidence
 - Degree of validity and reproducibility

Needed: A Rationale Communications Model

Approach to Developing Program

- Check list (bottom up):
 - Review what others have done and copy
 - Modify as needed
- Program Design (top down):
 - Develop Goals and Objectives
 - Select Tools to meet Goals and Objectives
 - Plan Evaluation

Suggest do top down and then bottom up: as a reality check

Info. Tools	Distribution	Purpose (strength)
Brochure	Physician	General Education
PPI	Package/ RPh	Risk Communication
Medication Guide	Package	Risk Communication and Methods of Hazard Avoidance
Informed Consent	Physician	Acknowledgement of Risks
Warning on Package	Package	Risk “signal”/compliance
Wallet Card	Starter Kit	Reminder
Stickers: Medication Vial or Prescription	Medication Vial or Prescription	Reminder or time sensitive control message
Patient Agreement or Contract	Physician	Behavioral Commitment
Decision Aid	Physician	Choice of Therapy
Video Tape or CD	Physician or Starter Kit	Persuasion or Emotion
Recurring Interventions (telephone calls)	Telephone	Behavioral Maintenance

Communications Process

Goal/Barrier

Measure

- | | |
|--------------|----------------------------|
| • Exposure | Distribution |
| • Attention | Readership |
| • Interest | Willingness to Read |
| • Understand | Comprehension |
| • Accept | Attitude Change |
| • Memory | Recall/Recognition Tests |
| • Decide | Decision Making Scenarios |
| • Behave | Intention to Heed/Behavior |
| • Learn | Behavior Maintenance |

*Select Vehicles to Maximize Communication Goal
May need a combination of Vehicles*

Sample Tactics Matrix

Goal Audience	Awareness	Motivation	Reinforcement
Sales	Detail Aid	Training manual	Leave behinds
CRM	Affirmative Scripts, Q&As	Training video	Desktop Media
MDs	Mailing	Sales Rep Material	Desktop Media, poster
ER	Sales force materials	Grand Rounds Training	Poster
Patients/ Partners	Waiting room placard, pharmacy printouts	Brochure/Web site, MD materials	Materials with logo

Theme: Risk Avoidance Involvement Logo as Reminder

Distributional Controls

Varying Levels of Control



Record
Keeping

Controlled
Substances

Special
Packaging

Actiq
Fosamax

Certification

Tikosyn

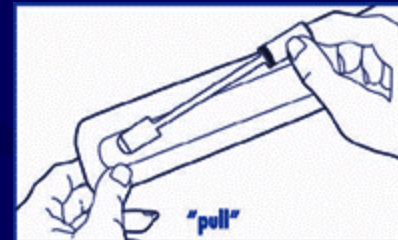
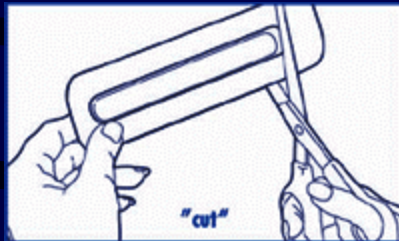
Prior
Approvals

Thalomid
Accutane

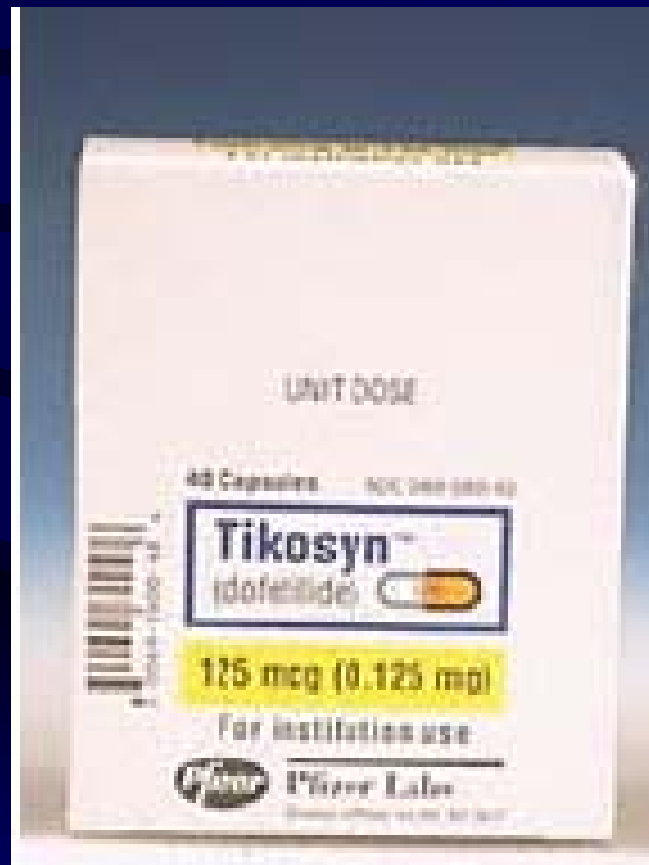
Closed
System

Clozaril

Actiq Packaging



Tikosyn



To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see **DOSAGE AND ADMINISTRATION**. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education

Tikosyn™ (dofetilide)
Education Confirmation Form for Institutions

Document Number
WCI2104

PRIMARY INSTITUTION INFORMATION			
Your Name			
Title/Position			
Institution Name			
Address 1			
Address 2			
City			
State	Zip	Please Print	
YOUR WORK PHONE		YOUR OFFICE FAX NUMBER	
		Must Provide Both	

I DESIGNATE THE FOLLOWING AFFILIATED IN-HOSPITAL PHARMACIES, IDENTIFIED BY DEA NUMBER(S) UNDER THIS AUTHORIZATION

PLEASE LIST THE DEA #(S) COVERED BY THIS AGREEMENT

DEA NUMBER(S)

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. The rate of Torsades de Pointes in trials of supraventricular arrhythmia patients was 0.8% (11/1346) when dosed according to their calculated creatinine clearance and the effect of TIKOSYN on QT and QTc. TIKOSYN is available only to hospitals and prescribers who have received the TIKOSYN dosing and treatment initiation education.

Please mail or fax this document to:

**TIKOSYN Education
Program Enrollment**
PO Box 917
1 Broad Ave
Fairview, NJ 07022
FAX (800) 788-2637

I confirm that the information on this form is correct. I understand that information will be used to enable Pfizer to identify institutions who are eligible to initiate and dispense TIKOSYN under this program. I understand Pfizer might share this information with others acting on its behalf and/or government agencies.

I further acknowledge that the appropriate staff (including telemetry nurses, pharmacists and physicians) in the institution have been educated on the treatment initiation and dosing for TIKOSYN. I am aware of the continuing need to have new staff educated on the treatment initiation and dosing for TIKOSYN and will ensure that such education occurs.

Please note that for outpatient prescriptions or refills, prescribers need to be a confirmed participant of a TIKOSYN education program.

Signature

Date

10599 WIF 01-27-00

This acknowledges your receipt of an appropriate TIKOSYN education program. If after receiving written confirmation of this registration you have a problem having a TIKOSYN order filled, call the number listed below. Written confirmation will be mailed to you promptly after receipt of this enrollment form.

1-877-TIKOSYN

WCI2104

Please tear off this stub and keep it for your records.

Please see full prescribing information in your TIKOSYN education materials.

I hereby acknowledge that I have received one of the appropriate TIKOSYN education programs. By providing the information on this form I further acknowledge the fact that this information is correct and will be stored by or on behalf of Pfizer to ensure that only prescribers who received appropriate education on the TIKOSYN treatment initiation and dosing guidelines can initiate TIKOSYN in a hospital setting and/or write TIKOSYN prescriptions. This information may be shared with government agencies.

PRIMARY OFFICE INFORMATION

Your Name						
Address #1						
Address #2						
City						
State	Zip	Professional Designation:	<input type="checkbox"/> MD	<input type="checkbox"/> DO	<input type="checkbox"/> PA	<input type="checkbox"/> NP

YOUR WORK PHONE**Must Provide Both****YOUR OFFICE FAX NUMBER****PRIMARY DEA NUMBER**

If you do not have a DEA #, you must provide your state license #. If you have both, please provide both.

PRIMARY STATE LICENSE NUMBER

PLEASE LIST ALL OTHER DEA NUMBERS (or additional state license numbers if you do not have a DEA #)

SECOND DEA NUMBER**STATE**

Please print your secondary state license number and state in the space provided

THIRD DEA NUMBER

If you have more than four DEA #s, please put a check in the box at the left.

STATE

Please print your tertiary state license number and state in the space provided

FOURTH DEA NUMBER**Hospital Affiliation Information**

In case you are affiliated with one or more hospitals, please fill in the information below, starting with your primary. If more than four affiliations, put a check in the box at the left.

PRIMARY

Hospital Name		
Address Line1		
Address Line2		
City	State	Zip

SECOND

Hospital Name		
Address Line1		
Address Line2		
City	State	Zip

THIRD

Hospital Name		
Address Line1		
Address Line2		
City	State	Zip

FOURTH

Hospital Name		
Address Line1		
Address Line2		
City	State	Zip

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. The rate of Torsades de Pointes in trials of supraventricular arrhythmia patients was 0.8% (11/1346) when dosed according to their calculated creatinine clearance and the effect of TIKOSYN on QT and QTc. TIKOSYN is available only to hospitals and prescribers who have received the TIKOSYN dosing and treatment initiation education.

PL10599 WPF 01-27-00

This acknowledges your receipt of an appropriate TIKOSYN education program. If after receiving written confirmation of this registration you have a problem having a TIKOSYN order filled, call the number listed below. Written confirmation will be mailed to you promptly after receipt of this enrollment form.

1-877-TIKOSYN**WCP3186**

Please tear off this stub and keep it for your records.

Practitioner Signature**Date**

Please mail or fax this document to:
TIKOSYN Education Program Enrollment

PO Box 917
1 Broad Ave Fairview, NJ 07022

FAX (800) 788 - 2637

Tikosyn Evaluation

Results The recommended starting dose was prescribed more frequently in the dofetilide group than in the sotalol group (79% vs 35%). A higher number of patients in the dofetilide group received the recommended baseline tests for potassium (100% vs 82%), magnesium (89% vs 38%), serum creatinine (100% vs 82%), and electrocardiography (94% vs 67%). A significantly greater proportion of patients in the dofetilide group received recommended electrocardiograms obtained after the first dose and subsequent doses

Conclusion Better adherence to several dosing and monitoring recommendations in the dofetilide group may be caused by the presence of the risk-management program. However, low usage of dofetilide during the study period may signify an unintended, negative consequence of the risk-management program.

Accutane RMP

- Accutane Approved 1982
 - Pregnancy Category X, Patient Brochure
- Pregnancy Prevention Program, 1998
 - Warning Labels, Informed Consent, Kit for Prescribers, Tracking Study to Assess Use of Kit, Patient Enrollment Survey,
- SMART Program October 2001
 - Enhanced Education, Physician Qualification, Yellow Stickers, Two Pregnancy Tests Prior to First Rx, Mandatory Pregnancy Testing Before Each Rx, Medication Guide, Two Forms of BC, 30-day Supply, No Refills, Develop Back-up Program for Mandatory Registries
- FDA Called All Manufacturers December 2003
 - Need to Modify RMP, Advisory Committee Meeting in February 2004
 - Current Program being modified (males included, blood testing record, patient qualification test)
- iPLEDGE Program August 2005
 - isotrotenian

Pregnancy Case Reports: Pre-S.M.A.R.T. vs. S.M.A.R.T.®

	Pre-S.M.A.R.T.	S.M.A.R.T.®
Total number	150	183
Treatment initiation date known	94	94
Treatment initiation date unknown	56	89

Number of Rxs decreased, rate did not change

Evolution of Accutane RiskMAP

Program Features	PPP	S.M.A.R.T	iPLEDGE
Registration of Physician		X	X
Registration of Patient			X
Registration of Pharmacy			X
Educational Component	X	XX	XX
Authorized Prescriber Check Mechanism		X	XX
Linking of Patient Ed./RM to Dispensing		X	XX
Linking of Pregnancy Test to Dispensing		X	XX
Limited to 30 Days Supply/No Refills		X	X
Use of Qualification Sticker		X	X
Auditing Mechanism		X	XX
Contraceptive Counseling	X	X	XX
Pregnancy Reporting	Decentralized	Decentralized	Centralized

Lotronex

Warning: Serious GI adverse events, some fatal, have been reported with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, blood transfusion, surgery, and death.

Restricted Conditions for the Use of LOTRONEX[®] (alosetron HCl) Tablets

- **Approved for reintroduction on June 7, 2002**
- **Under new Risk Management Program, restrictions include:**
 - **Updated warnings in the complete Prescribing Information, including a Medication Guide for patients that explains to patients what to do if they get constipated or have signs of ischemic colitis**
 - **A lower starting dose than previously approved**
 - **A prescribing program for physicians to be enrolled in, based on self-attestation of qualifications and acceptance of certain responsibilities in prescribing LOTRONEX**

PRESCRIBING PROGRAM FOR LOTRONEX™:

PHYSICIAN ATTESTATION OF QUALIFICATIONS AND ACCEPTANCE OF RESPONSIBILITIES

I wish to participate in the Prescribing Program for LOTRONEX and by my signature below, attest that I have the qualifications and accept the responsibilities described below.

- I understand that for safety reasons LOTRONEX® (alosetron hydrochloride) is approved with marketing restrictions of which the Prescribing Program for LOTRONEX is a required element.
- I understand that because of serious gastrointestinal adverse events, some fatal, associated with this drug, LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms generally lasting for 6 months or longer, had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and who have failed to respond to conventional therapy. Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following: (1) frequent and severe abdominal pain/discomfort; (2) frequent urgency or fecal incontinence; or (3) disability or restriction of daily activities due to IBS. Less than 5 per cent of IBS is considered severe.
- I understand that treatment benefits of LOTRONEX in populations other than adult women with diarrhea-predominant IBS have not been established.
- I have reviewed the complete prescribing information for LOTRONEX and am thoroughly familiar with the important information in the Boxed Warning, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration, and Medication Guide sections. I have also reviewed and am familiar with all the components of the Patient-Physician Agreement for LOTRONEX.
- I can diagnose and treat IBS.
- I can diagnose and manage ischemic colitis.
- I can diagnose and manage constipation and complications of constipation.
- I understand the risks and benefits of treatment with LOTRONEX for severe diarrhea-predominant IBS, including information in the package insert, Medication Guide, and Patient-Physician Agreement.
- I will educate any patient who is considering treatment with LOTRONEX on the risks and benefits of treatment with LOTRONEX and obtain the patient's signature on the Patient-Physician Agreement form, sign it, place the original signed form in the patient's medical record, and give a copy to the patient.

LOTRONEX® (alectrocin HCl) Tablets

The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX®

02/15/16

10/09/16

Pharmacist dispenses Retail Pack for LOTRONEX, which includes the required Medication Guide, Package Insert, Medicine, and Survey Enrollment Form for the Follow-Up Survey for LOTRONEX

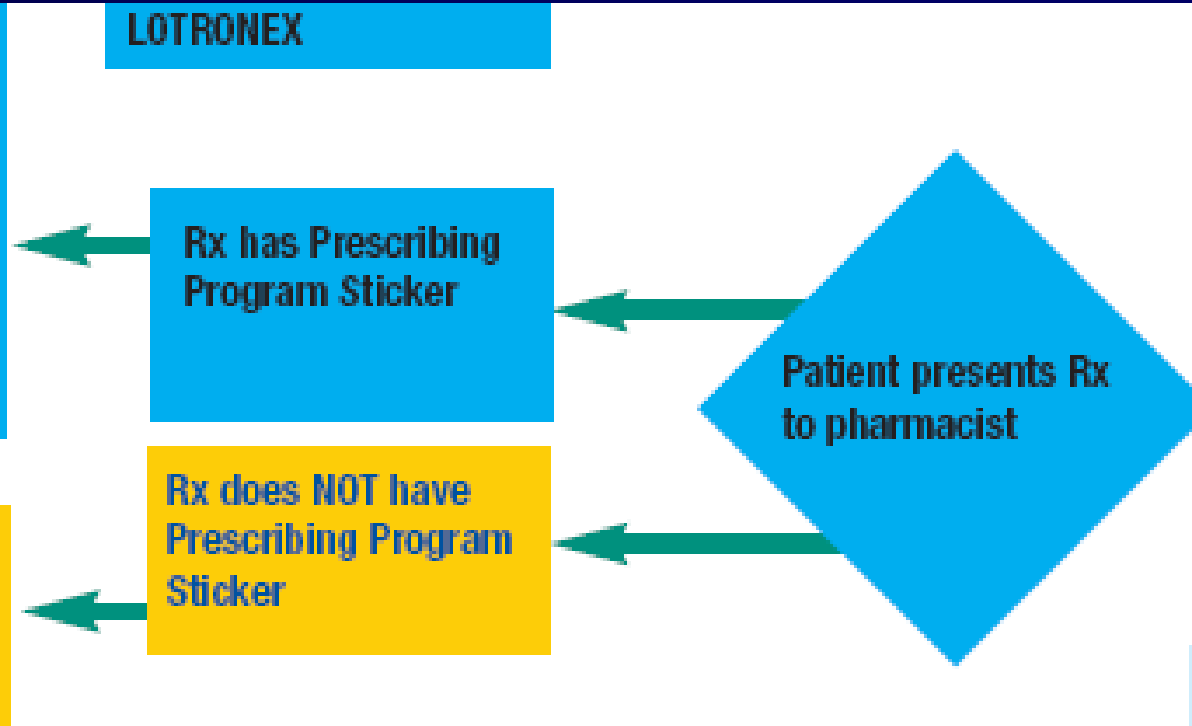
Pharmacist does NOT dispense LOTRONEX and refers patient back to physician

LOTRONEX

Rx has Prescribing Program Sticker

Rx does NOT have Prescribing Program Sticker

Patient presents Rx to pharmacist





Posted 5/5/2004 1:14 AM

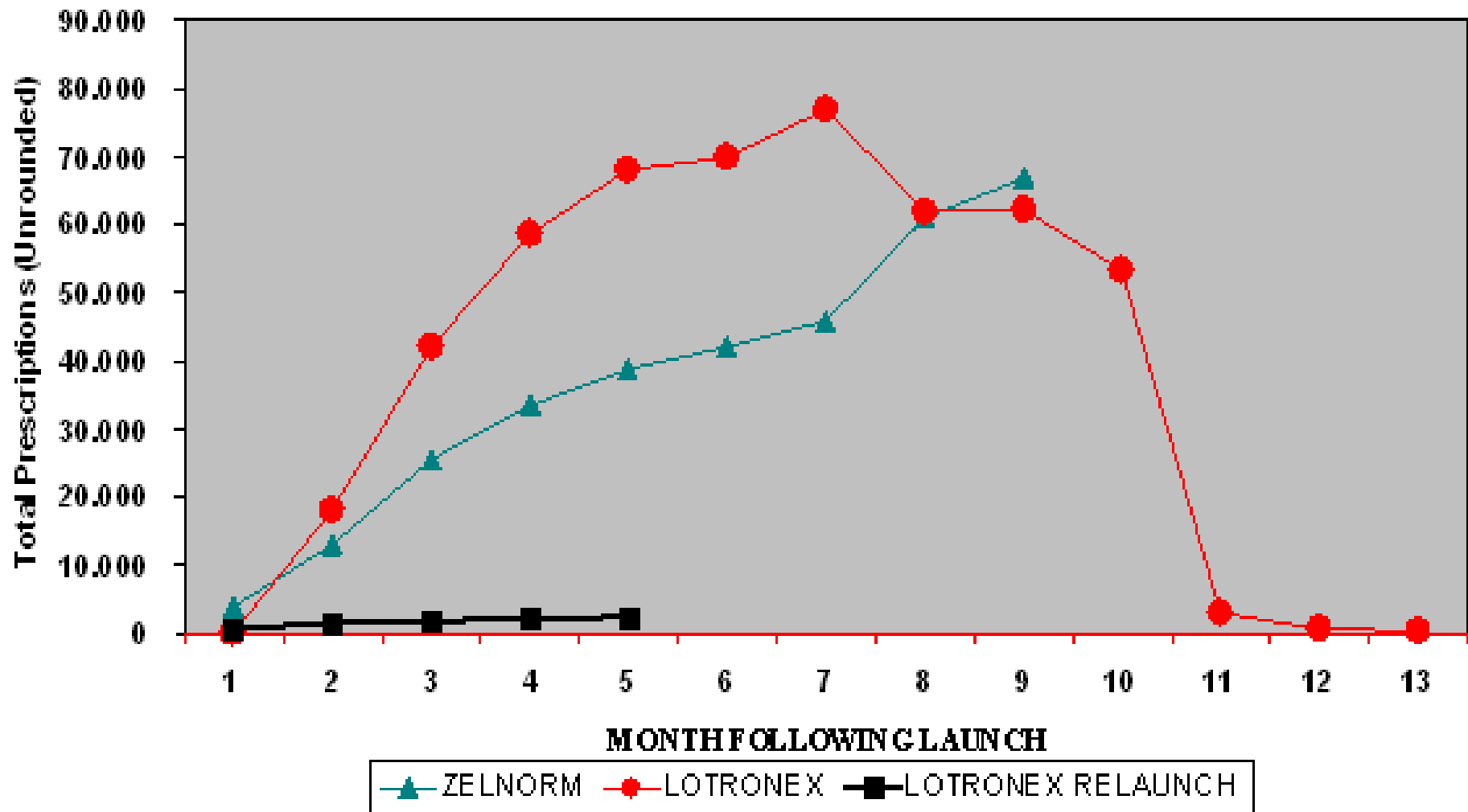
Fears cited for IBS drug's lagging sales

By Rita Rubin, USA TODAY

Sales of Lotronex, a drug to treat irritable bowel syndrome that was temporarily taken off the market because of safety concerns, have been far lower than expected since its reintroduction in November 2002, its maker says.

GlaxoSmithKline attributes Lotronex's disappointing sales to the Risk Management Program required by the Food and Drug Administration. The program, which is designed to reduce the risk of potentially life-threatening side effects, requires that doctors attest that they are qualified to prescribe Lotronex. Doctors and pharmacists also are supposed to give patients an FDA-approved Medication Guide before they start taking Lotronex.

Sales (TRx) Following Launch

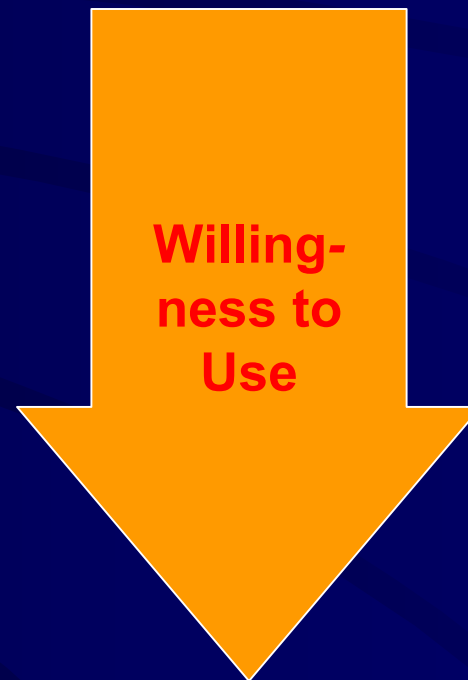


Risk Management Irony

Beliefs

$$\left\{ \text{Safety} = \frac{\text{Benefits}}{\text{Risks}} \right\}$$

Perceptions



*Communications do more than inform, they modify
modify beliefs, may change perceptions*

The Comfort Zone

MD Perceptions:

Too little RM

Drug may hurt patient

Too risky to try

Comfort
Zone

Will benefit and
Protect patient,
Willing to try



Too Much RM

Personal Liability

Too much work to use

Oxycontin: MAADO

- 1) extensive **education** of prescribers, pharmacists and patients on proper pain management and the safe use of OxyContin in appropriate patients.
- 2) active **surveillance** to detect signals of abuse, diversion, addiction and overdose. The company's RADARS(R) System can detect signals down to the three digit zip code in specific geographic areas.
- 3) a wide range of **interventions**, including support and education of law enforcement, targeted education of healthcare professionals on combating diversion and abuse, and awareness and prevention programs to the public in affected communities about the dangers of prescription drug abuse.

Misuse, Abuse, Addiction, Diversion and Overdose

Clozapine RMP

- Black Box Warning
 - Agranulocytosis, Seizures, Myocarditis
- No Blood No Drug Monitoring
 - Relaxation from QW to QOW
- Pharmacy Registry
- Patient Registry
- Physician Registry

Thalidomide RMP

- S.T.E.P.S. Program Elements
 - Required Pregnancy Testing
 - Required Birth Control Measures
 - Physician Education
 - Patient Education
 - Registration
 - Patient Informed Consent Forms
 - Restricted Distribution System

Patented Program: Isotretinoin to License Procedures

Controlled Distribution

- MD always Controls Distribution
- Additional Limitations by controlling
 - Who prescribes, dispenses, uses
 - Conditions of Use
 - MD with enhanced limitations
 - Necessary testing
 - Necessary knowledge qualifications
 - Necessary evaluation

Distribution Limitations

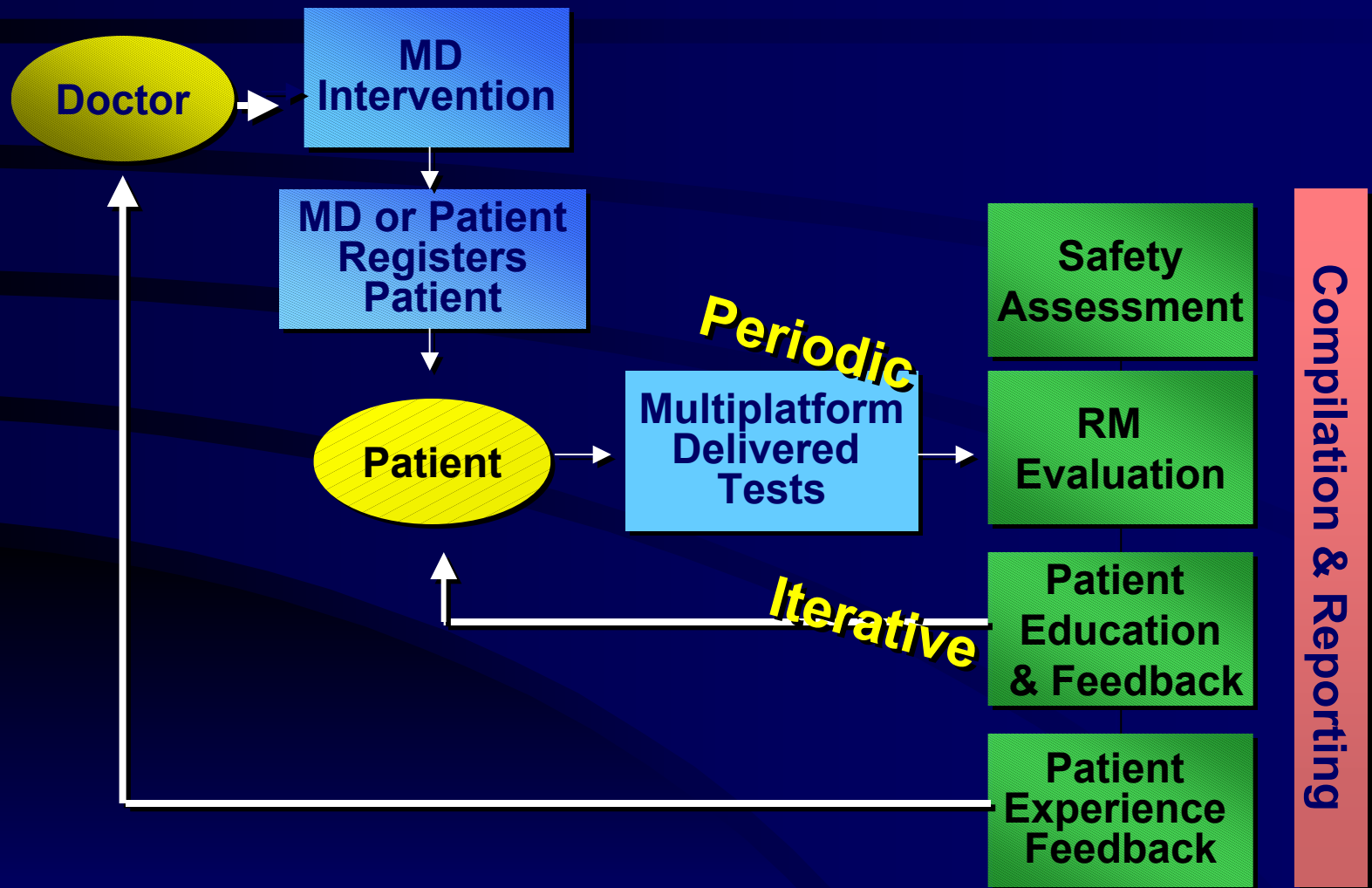
	Existing Qualification	Additional Training	Self-Attestation	Manufacturer sets conditions
MD	Limited to medical specialty	CE training	Letter of Understanding	Must use sticker
Pharm-acy	Limited to specialty pharmacy	Drug Administration	Agreement Signed	Controlled Access
Patient	No pre-existing condition	Qual. check (knowledge self-admin)	Consent or Agreement	Must join registry

Mandatory vs. Voluntary Debate

System Enhancements

- Focus on Outcomes, not Process
 - Measure knowledge and provide feedback where needed
 - Immediate: programmed learning
 - Personalized form to patient
 - Customized form to MD (patient experience model)
- Integration of safety assessment and risk minimization

Multi-Function Registry



Multifunction Registry

- Survey Risk Knowledge, Attitudes, Intentions
 - Provide Individual Feedback to MD/Patient
- Survey to Evaluate RM Intervention
 - Combine data to evaluate Impact
- Measure Hypothesized ADEs in Registry
- Survey forms carefully designed to avoid question-asking biases

Create Specialized Benefit-Risk Database

Black Box as a Signal

QUOTE OF THE DAY

"Having a black box on the label is a big deal. It's pretty astounding to go from a year ago thinking this is one of the most benign drugs to a 180-degree turn in the opposite direction." Dr. Susan Hendrix, a gynecologist, on the government decision to require warning labels on drugs containing estrogen.

What can we do in the Drug Development Process to Plan for Appropriate Use? (1)

- Collect safety data, better identify and quantify drug risks
- Understand the Provider and User
 - Assumptions, perceptions and beliefs
 - How the drug will be used in practice
 - Willingness to accept messages
- Test Interventions
 - Comprehension Testing of Messages and Tools
 - Include Program in Phase III Trials

What can we do in the Drug Development Process to Plan for Appropriate Use? (2)

- Develop rationale for plans/questions (patient and provider surveys)
- Validate Evaluation Questionnaires (e.g., patient knowledge, beliefs)
- Develop initial registry (rollover to phase IV)
- Create advisory board – patients, physicians

Continuous Quality Improvements

- Seek to avoid All or None Reactions
 - Add more/redesign tools if current ones not working
- Seek to “diagnose” cause for failures
 - Redesign interventions based on data
- Form Committees
 - Working Committee
 - Oversight and Review
 - Periodic Meetings
 - Each 6 months

Benchmarking Success:

Seek to improve over time, avoid setting an a priori level

Conclusion

- FDA guidance is reasonable and responsive to public input
- Companies must begin to adapt their thinking to incorporate risk minimization
 - Ball is in pharma's court – develop best practices, plan for RM during drug development
 - FDA will design Risk Minimization Plans if pharmaceutical companies do not
- Still in a period of learning, not a lot of successes
 - Innovation and evaluation is needed
 - Vioxx Fallout—look for more stringent reviews