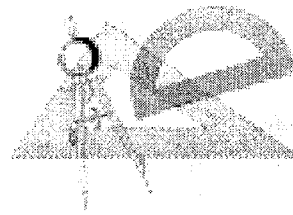


Engineering a Risk Management Program



1

Rationale

- Drug use of Accutane among women of childbearing potential is escalating
- In spite of all the Sponsor's efforts to communicate Accutane's teratogenic potential there is still limited compliance with
 - Pregnancy testing before exposure
 - Pregnancy testing during exposure
 - Appropriate use of contraception

2

Rationale

- Measures of pregnancy exposures and outcomes based on the Slone Survey and spontaneous case reports are not representative
 - Participation in Slone Survey is incomplete (<40%)
- Increasing numbers of women exposed to Accutane increases the absolute number of pregnancy exposures

3

Goals of Risk Management Program

- No one starts Accutane if pregnant
- Avoid pregnancy during therapy
- Monitor to assure these goals are met

4

Goals	Design 1	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant					
Avoid Pregnancy During TX					
Monitor to assure these goals are met					

5

Elements of a Pregnancy Risk Management Program

- Education
- Informed consent
- Complete participation
- Tracking of pregnancy exposures
- Compliance with pregnancy prevention practices
- Restricted distribution to pharmacies

6

Elements	Design 1	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent					

7

Education/Informed Consent

- To communicate the risk associated with pregnancy exposure
- Should include patients, physicians, pharmacists and other health care professionals
- Emphasize the importance of compliance with program requirements
- Via labeling, printed materials, videos, physician counseling, CME, etc.

8

Elements	Design 1	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent					
Complete Participation *Registration					

9

Complete Participation

- All patients should benefit from the protection provided by a comprehensive Pregnancy Prevention Program
- Registration of program participants will
 - Provide a denominator
 - Serve as a platform for other interventions directed to assure compliance with pregnancy prevention practices

10

Elements	Design 1	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent					
Complete Participation <i>*Registration</i>					
Tracking of Pregnancy Exposures <i>*Pregnancy Registry</i> <i>*Surveys</i> <i>*External Data</i>					

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Tracking of Pregnancy Exposures

- **Pregnancy Registry**
 - Tracking system of pregnancy exposures/outcomes
- **Survey of PPP participants**
 - Slone Survey
- **External Data Sources**
 - Supplemental source of pregnancy exposures/outcomes independent from Pregnancy Prevention Program

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Elements	Design 1	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent					
Complete Participation *Registration					
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data					
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention					

13

Optimal Compliance with Pregnancy Prevention Practices

- Essential to minimize the risk of exposure
- Engineered into Pregnancy Prevention Program to ensure that goals are met
 - Linkage between a negative pregnancy test/other core Pregnancy Prevention Program elements and the dispensing of Accutane
 - Physician documents negative test
 - Pharmacists verifies that negative pregnancy test has been documented

14

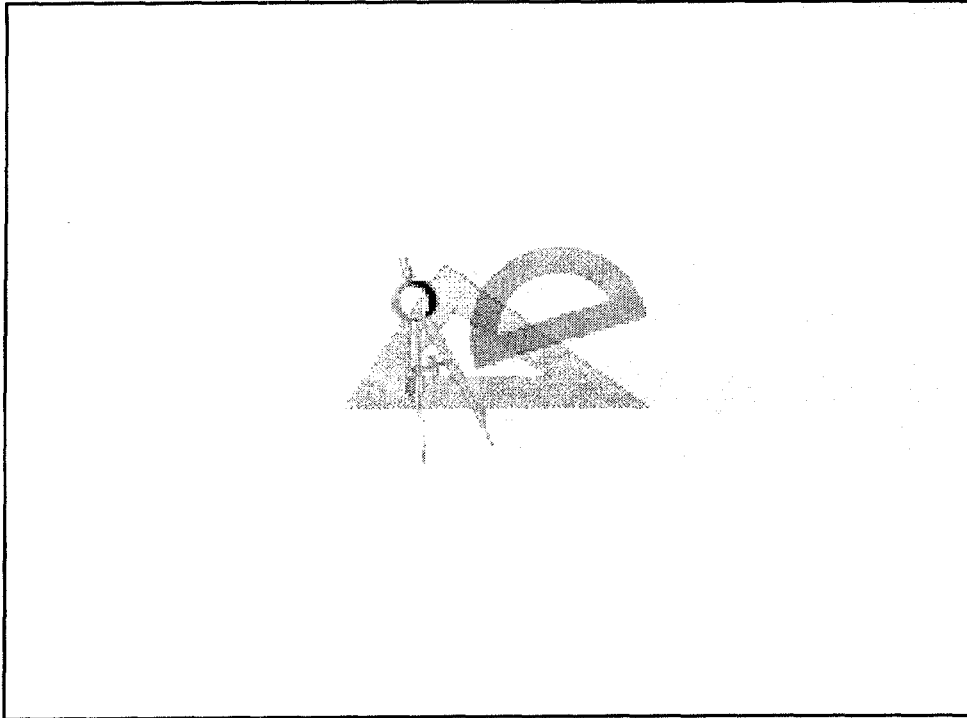
Elements	Design 1	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent					
Complete Participation *Registration					
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data					
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention					
Restricted Distribution to Pharmacies					

15

Restricted Distribution to Pharmacies

- Additional safeguard against inappropriate use and dispensing
- Restrictions on pharmacies to assure compliance with dispensing constraints
 - Pharmacies would have to be registered and comply with dispensing requirements to be authorized to dispense Accutane

16



17

Elements	Design 1 Roche's Proposal	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent	X				
Complete Participation *Registration					
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data	X X				
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention					
Restricted Distribution to Pharmacies					

18

Design 1 (Roche Proposal)

- Education and informed consent
 - Major improvements of PPP Kit
 - Labeling changes
- Tracking Pregnancy Exposures
 - Slone Survey
 - Promote enrollment and expand
 - Roche Safety Database
 - More information on each patient

19

Design 1 (Roche Proposal)

- Compliance
 - Supply all urine pregnancy test kits

20

Design 1 (Roche Proposal): Pros

- Intensifies efforts to educate participants
 - Stresses the importance of pregnancy testing, use of adequate contraception and survey enrollment
- Patient urine pregnancy tests kits
 - May increase the frequency of testing before and during therapy
 - May result in earlier identification of pregnancies and reduce the length of in-utero exposure to Accutane

21

Design 1 (Roche Proposal): Pros

- Meets part of Monitoring Goal
 - Provides some data on pregnancy exposure/outcomes

22

Design 1 (Roche Proposal): Cons

- Participation in the program by patients and physicians is still *voluntary*
- Compliance with program components is voluntary and incompletely measured
- Measurement of pregnancy exposures and outcomes is limited

23

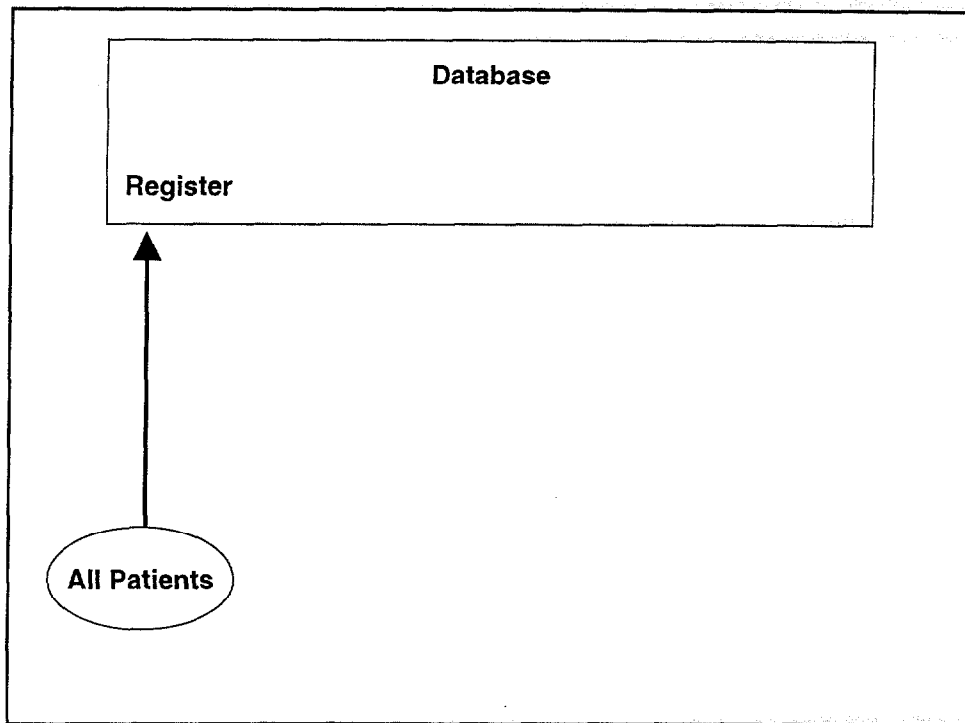
Design 1 (Roche Proposal): Cons

- No documentation of program compliance (e.g., negative pregnancy test) prior to Accutane dispensing
 - Non participants can still prescribe without constraints
 - Does not address other elements of compliance (e.g., adequate use of contraception)

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Elements	Design 1 Roche's Proposal	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent	X	X			
Complete Participation *Registration [Patients]		X			
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data	X X	X X X			
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention					
Restricted Distribution to Pharmacies					

25



26

Design 2

- Tracking Pregnancy Exposures
 - Slone Survey
 - Pregnancy registry for all identified exposures
 - Independent surveillance of pregnancy exposure via monitoring programs
 - Example: OTIS Network

27

Design 2: Pros

- Meets part of Monitoring Goal
 - Denominator is known
 - Tracking of pregnancy exposures enhanced by additional independent external sources of data

28

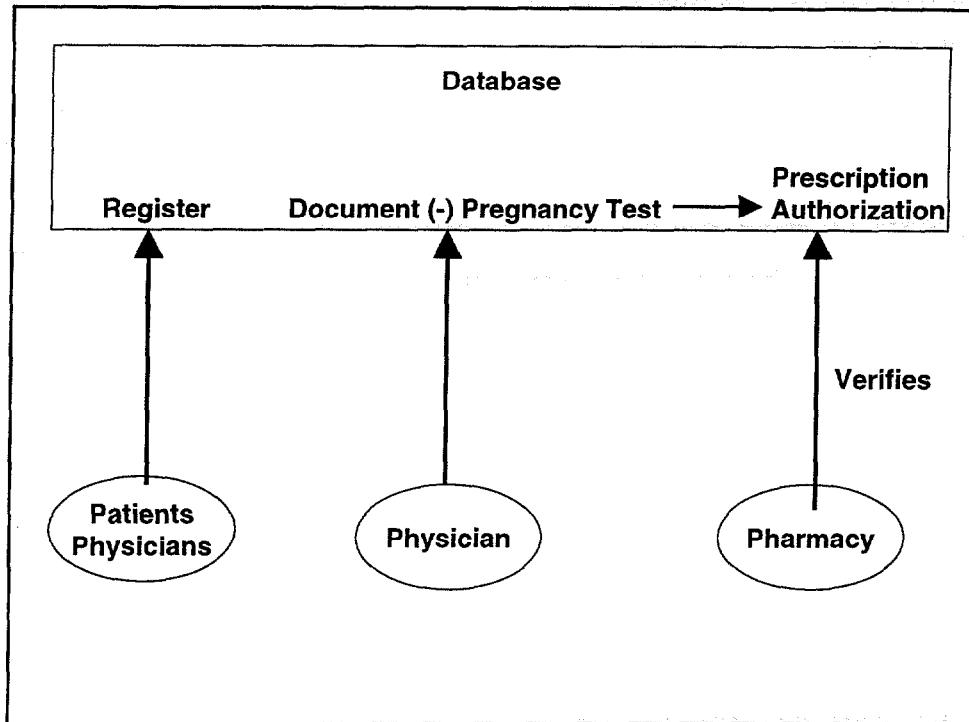
Design 2: Cons

- Risk management goals not met
 - Pregnant women could still be started on Accutane
 - Women could become pregnant during treatment with Accutane
 - Monitoring is still incomplete
- Need to create a database
- Burden on female patients to be registered

29

Elements	Design 1 Roche's Proposal	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent	X	X	X		
Complete Participation *Registration [Patients/Physicians]		X	X		
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data	X X	X X X	X X X		
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention			X		
Restricted Distribution to Pharmacies					

30



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Design 3: Pros

- Meets our first goal
 - Provides a mechanism to confirm that female patients are not pregnant prior to dispensing of Accutane
- Meets part of our second goal
 - Avoids pregnancy exposure by testing
- Meets our third goal
 - Monitoring of pregnancy exposures becomes comprehensive by linkage mechanism

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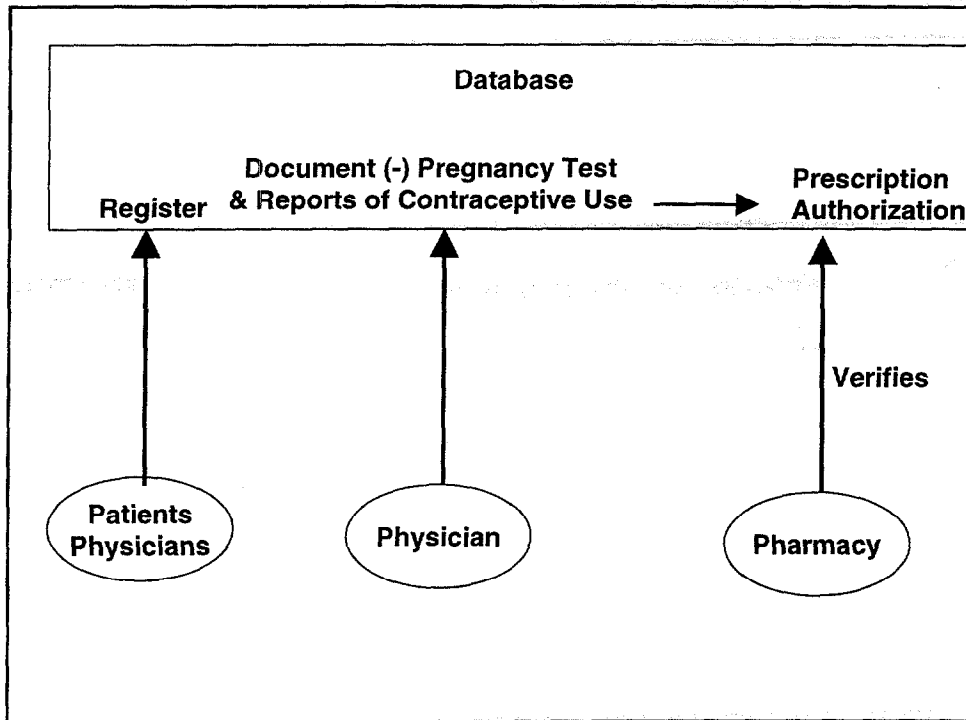
Design 3: Cons

- Compliance with effective contraception is not considered
- Need to create a database
- Burden
 - All physicians and patients are registered
 - Pharmacists are required to validate negative pregnancy status before dispensing

33

Elements	Design 1 Roche's Proposal	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent	X	X	X	X	
Complete Participation *Registration [Patients/Physicians]		X	X	X	
Tracking of Pregnancy Exposures *Pregnancy Registry *Surveys *External Data	X X	X X X	X X X	X X X	
Optimal Compliance Via Linkage *Pregnancy Testing *Other Elements for Pregnancy Prevention			X	X X	
Restricted Distribution to Pharmacies					

34



35

Design 4: Pros

- All goals are met
- Avoids pregnancy exposure 2 ways
 - Testing for pregnancy
 - Contraceptive counseling

36

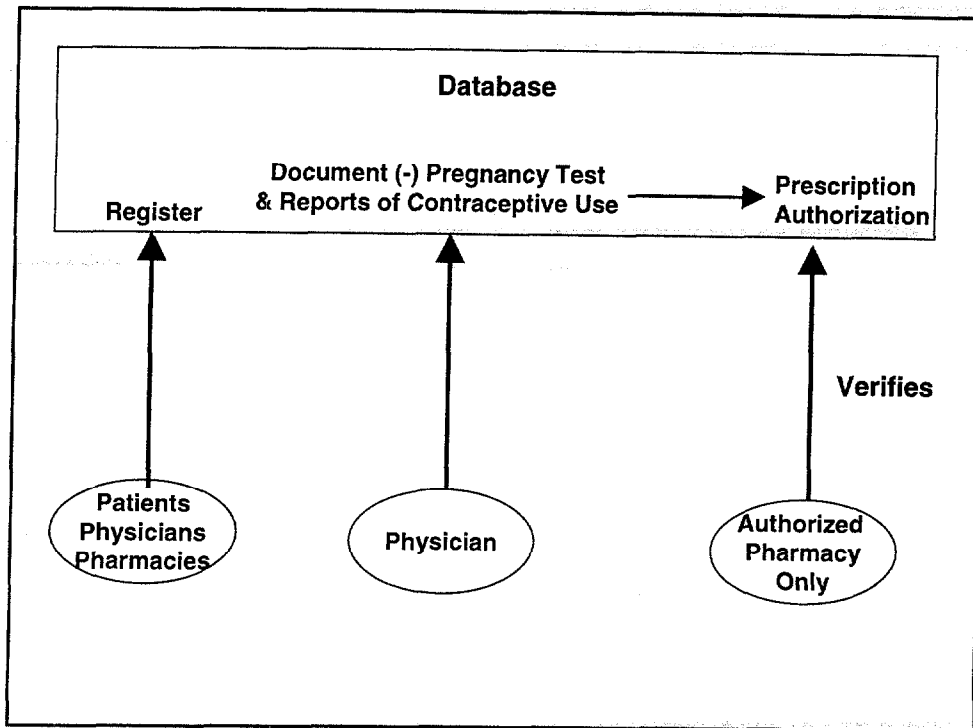
Design 4: Cons

- Need to create a database
- Burden
 - All physicians and patients are registered
 - Pharmacists are required to validate negative pregnancy status before dispensing
 - Requires more private information from patients

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Elements	Design 1 Roche's Proposal	Design 2	Design 3	Design 4	Design 5
Education & Informed Consent	X	X	X	X	X
Complete Participation *Registration [Pat./Phys./Pharma.]		X	X	X	X
Tracking of Pregnancy Exposures					
*Pregnancy Registry	X	X	X	X	X
*Surveys	X	X	X	X	X
*External Data		X	X	X	X
Optimal Compliance Via Linkage					
*Pregnancy Testing			X	X	X
*Other Elements for Pregnancy Prevention				X	X
Restricted Distribution to Pharmacies					X

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Design 5: Pros

- All goals are met
- Additional safeguard against inappropriate use and dispensing

40

Design 5: Cons

- Need to create a database
- Burden
 - All physicians and patients are registered
 - Pharmacists are required to validate negative pregnancy status before dispensing
 - Requires more private information from patients
 - Requires pharmacies to be registered and certified

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Design 5: Cons

- Restricts distribution
- Decreases access to drug
 - May encourage alternate sourcing

42

Which goals are met by each Design?

43

Goals	Design 1 Roche Proposal	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant					
Avoid Pregnancy During TX					
Monitor to assure these goals are met	+/-				

44

Goals	Design 1 Roche Proposal	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant					
Avoid Pregnancy During TX					
Monitor to assure these goals are met	+/-	+/-			

45

Goals	Design 1 Roche Proposal	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant			+		
Avoid Pregnancy During TX			+/-		
Monitor to assure these goals are met	+/-	+/-	+		

46

Goals	Design 1 Roche Proposal	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant			+	+	
Avoid Pregnancy During TX			+/-	+	
Monitor to assure these goals are met	+/-	+/-	+	+	

47

Goals	Design 1 Roche Proposal	Design 2	Design 3	Design 4	Design 5
No one starts Accutane if Pregnant			+	+	++
Avoid Pregnancy During TX			+/-	+	++
Monitor to assure these goals are met	+/-	+/-	+	+	+

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Conclusions

- Sponsor's proposal will not achieve 3 core goals of a Pregnancy Prevention Program
- Other program designs provide an opportunity to achieve FDA's public health goals

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Point to Consider

- How should we balance the achievement of FDA goals with burden?

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