

# Accutane and Pregnancy Exposure

9/18/2000

## Regulatory History Accutane

- 1982
  - Accutane approved as: Pregnancy Category X
  - Label described risk of teratogenicity
    - Contraindications
    - Warnings
    - Precautions
  - *Patient Information Brochure* also contained warnings about avoiding pregnancy

## Regulatory History Accutane

- **1983**
  - First report of infant born with malformations
    - Label changes
    - First *'Dear Doctor'* letter
    - Second *'Dear Doctor'* letter with additional information about the reported cases
  - Sponsor distributes red stickers to pharmacies with further warnings

## Regulatory History Accutane

- **1984**
  - Labeling changes
  - Third *'Dear Doctor'* letter
- **1984 to 1988**
  - Roche issued seven *'Dear Doctor'* letters
- **1988**
  - Advisory Committee Meeting
  - Roche introduced the concept of the Accutane Pregnancy Prevention Program (PPP)

## **Accutane PPP**

- Boxed Warning
- Informed Consent for Female Patients
- Warnings on Package
- PPP Kit for Prescribers
- Multiple Other Educational Efforts
- Accutane Tracking Study
- Patient Enrollment Survey (Slone Survey)

## **Accutane PPP**

- Boxed Warning
  - Strict qualifications for Rx to females
  - Pregnancy testing
  - Two reliable methods of contraception
    - 1 month before Tx
    - During Tx
    - 1 month after Tx
  - Instructions to begin Tx on the 2-3 days of next menstrual period

## **Accutane PPP**

- **Boxed Warning**
  - Negative pregnancy test within one week before starting therapy
  - One month prescription supply
  - Monthly pregnancy testing and monthly contraceptive counseling

## **Accutane PPP**

- **Informed Consent for Female Patients**
- **Warnings on Package**
  - Blister packaging with avoid pregnancy sign



## **Accutane PPP**

- **PPP Kit for Prescribers**
  - Pregnancy Counseling Materials
  - Patient Information Brochure
  - Information on the *Patient Referral Program*
  - Toll-Free-Number
- **Other Educational Efforts**
  - CME courses
  - Training video for residency programs

## **Accutane PPP**

- **Accutane Tracking Study**
  - Evaluates physician's usage of Roche's PPP Kit and other core components of the PPP
- **Patient Enrollment Survey (Slone Survey)**
  - Independent follow-up survey conducted by the Slone Epidemiology Unit at Boston University School of Public Health

## **Accutane Tracking Study**

- Description
  - Telephone Survey
  - Includes 110 dermatologists and 200 primary care physicians
- Purpose
  - Determine usage of PPP components
- Limitations
  - Tracks physicians' perceptions of PPP use rather than actual use

## **Accutane PPP - Slone Survey**

- Voluntary survey of women treated with Accutane since 1989
- Seeks to measure
  - Patient's knowledge of Accutane's teratogenic risk
  - Compliance with PPP components
  - Pregnancy exposure rates of enrollees
  - User profile
    - Risk factors for pregnancy exposure

## **Accutane PPP - Slone Survey**

- Captures 30-40% of women treated with Accutane

## **Accutane PPP**

- Tools to monitor the impact of the PPP on the occurrence of pregnancy exposure
  - Slone Survey
  - Accutane Tracking Study
  - Case Reports

## **Roche/FDA's Concerns**

- Both Roche and FDA have evaluated this program's performance and concluded that there are specific areas of the program which need to be strengthened

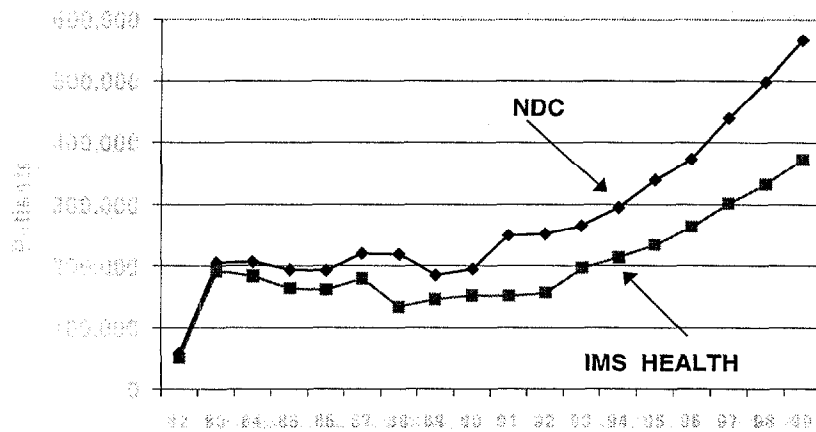
## **Areas of Concern**

- Patterns of Drug Use
- Performance Characteristics of the PPP
  - Slone Epidemiology Unit Survey Data
  - Accutane Tracking Study
- Case Report Data

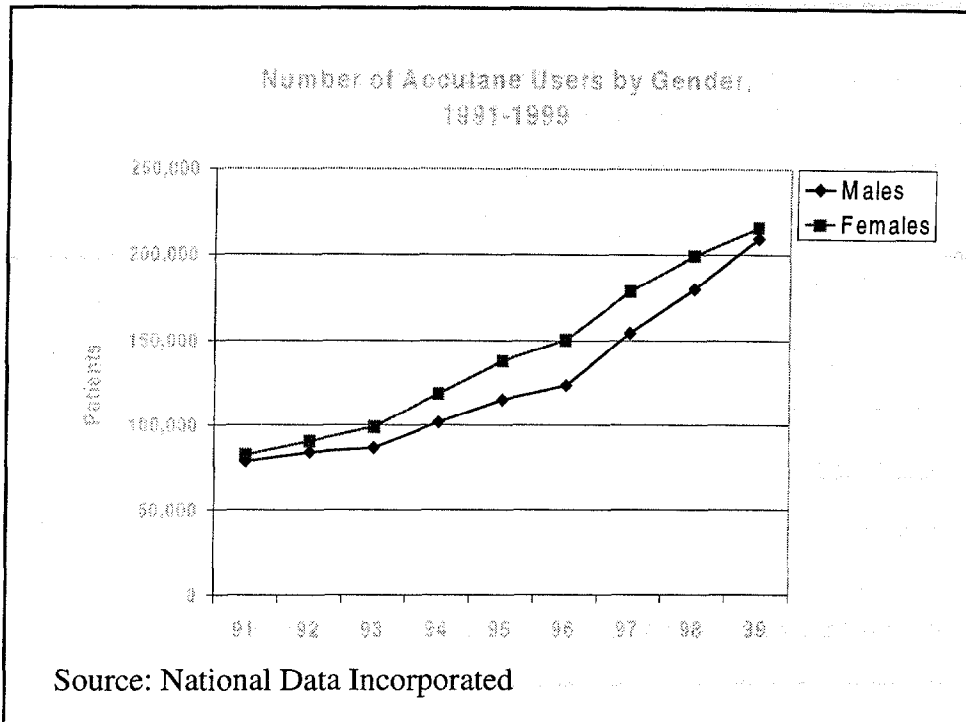


## Drug Utilization Data

Estimated Number of Patients Treated with  
Acquasine by Year, 1982-1999



Source: IMS HEALTH, NDI & NPA Plus and National Data Incorporated



## Drug Use Data: Summary

- Use in women approximates use in men
- Accutane use in women has increased > **200%** between 1992 and 1999
- **85-90%** of women using Accutane are aged 15-44
- Among women 15-44, **80%** of use is below age 30

## Slone Survey

### Distribution of Women Enrolled in Slone Survey by Pregnancy Risk Category, 95-99

Pregnancy Risk Category	%
Sexually Active	40
Using Birth Control	39
Not Using Birth Control	1
Not Sexually Active	57
Using Birth Control	25
Not Using Birth Control	32
Other	4
Hysterectomy or Postmenopausal	3
Unknown	1

## Non-Compliance with Roche's Pregnancy Prevention Program, 95-99

PPP Element	Percent
Did Not Report Signing Consent	23
Did Not Report Having a Pregnancy Test Before TX	25
Did Not Report Postponing TX for Pregnancy Test Results	33
Did Not Report Postponing TX to Next Menstrual Period	43
Did Not Report Having a Pregnancy Test During TX	40

## Accutane Exposed Pregnancies Identified in the Slone Survey, 89-00

<b>Exposed Pregnancies</b>	<b>958</b>
<b>Pregnancy Outcomes</b>	
<b>Terminations</b>	<b>834</b>
Elective	644
Spontaneous	164
Ectopic	26
<b>Live Births</b>	<b>110</b>
<b>Unknown</b>	<b>14</b>

## Slone Survey

- Congenital Anomalies
  - Pregnancies resulting in Live Births = **110**
  - Total # of infants born= **111\***
  - Number of infants with available medical record or who were examined = **60**
    - **8/60** (13%) showed major malformations

\*Including one set of twins

## Pregnancy Rates Among Slone Survey Enrollees

Year	Rate/1,000 person-years	Est.# of Pregnancy Exposures
1991	7.8	231
1992	7.7	244
1993	7.1	251
1994	6.2	241
1995	7.4	342
1996	7.0	355
1997	6.3	368
1998	5.6	359

## **Slone Survey: Summary**

- Pregnancies are still occurring
- Substantial non-compliance with critical elements of Accutane PPP is well documented
- Representativeness of survey unlikely
  - Voluntary, captures less than 40% of all users

## **Accutane Tracking Study**

## **Accutane Tracking Study Results**

- Physicians do not use all the elements included in the kit because:
  - They feel oral communication is adequate
  - Feel kit is inconvenient to them
- High use of product brochure
- Slight increase over time in the report of pregnancy testing and use of consent form

## **Case Reports**

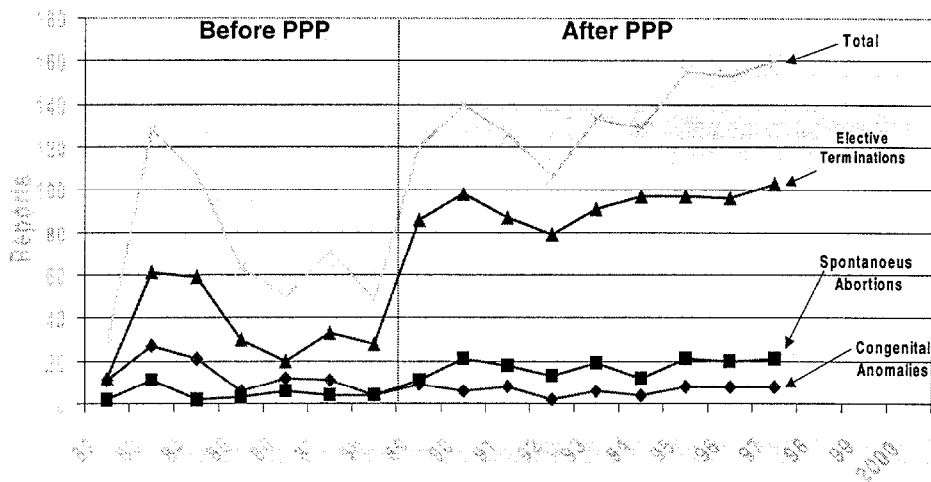
## Limitations of Case Reports

- Only a small percentage of adverse drug events are recognized and reported to FDA
- Reporting of adverse drug events typically declines over the marketing history of a drug product

US Pregnancy Reports by Outcome and Year of Therapy.

Roche Safety Database 1982-1997

(Note: 1982 data is incomplete due to reporting lag.)





## Accutane Pregnancy Exposures, Roche Data 1982-2000

<b>Exposed Pregnancies</b>	<b>1,995</b>
<b>Pregnancy Outcomes</b>	
<b>Terminations</b>	<b>1,446</b>
Elective	1,214
Spontaneous	213
Missed	19
<b>Live Births</b>	<b>383</b>
<b>Unknown</b>	<b>166</b>

## Roche Safety Database 1982-2000

- Congenital Anomalies
  - Pregnancies resulting in Live Births = 383
  - Infants with Congenital Anomalies = 162  
(42%)

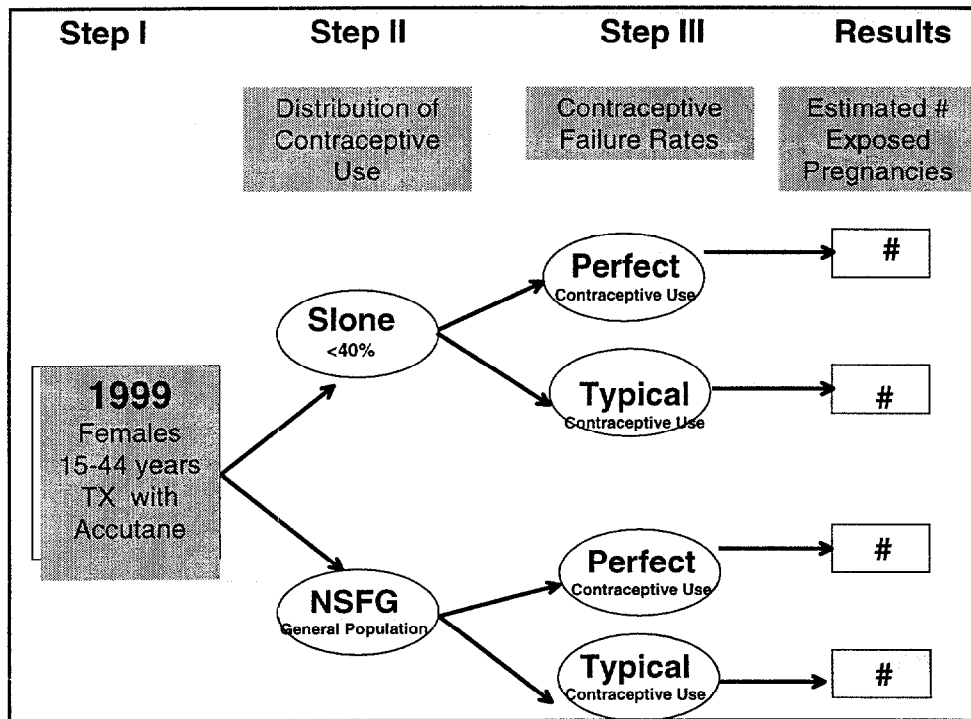
## **Estimated Rates of Congenital Anomalies in Accutane Exposed Pregnancies Resulting in Births**

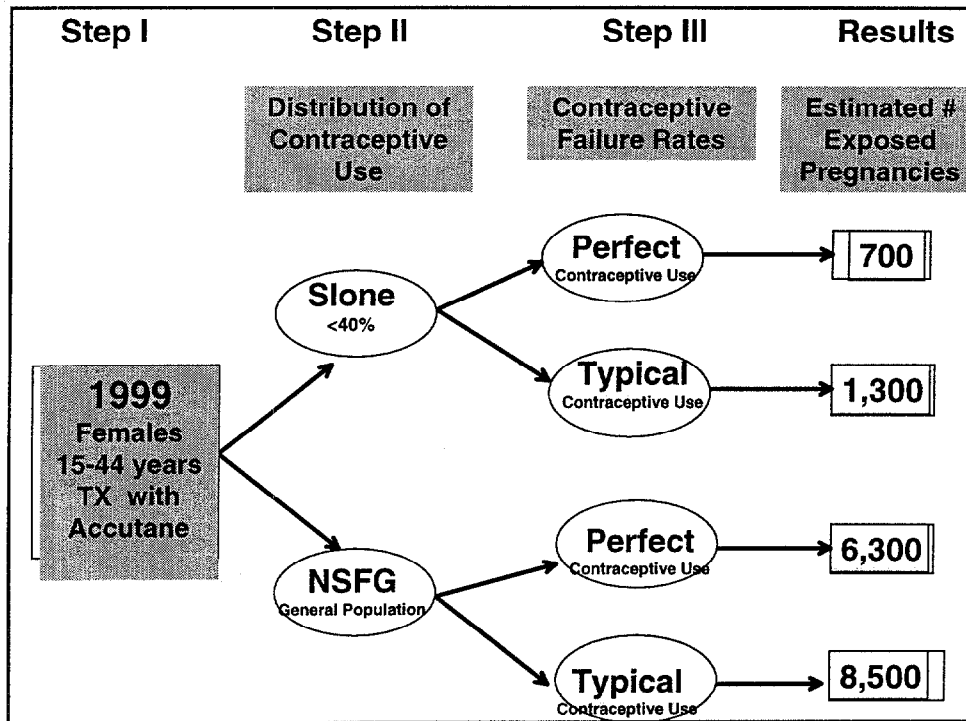
	<b>Congenital Anomaly Rate</b>
<b>Adverse Event Reports</b>	<b>42%</b>
<b>Literature</b>	<b>25%</b>
<b>Voluntary Survey</b>	<b>13%</b>

## **Case Report: Summary**

- Pregnancy exposures reported to Roche and FDA are not declining
- 1,995 exposed pregnancies documented by Roche since approval
  - 1,446 since Accutane® PPP inception
- Congenital anomalies continue to be reported to Roche and FDA

# Pregnancy Exposure Model





## Model: Summary

- Estimated pregnancy exposures in 1999
  - 700 - Slone Survey contraceptive distribution/perfect use
  - 1,300 - Slone Survey contraceptive distribution/typical use

## Conclusions

- 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

## Conclusions

- 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