

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: PID D030417
Drug: Isotretinoin
Topic: Pregnancy Exposures

EXECUTIVE SUMMARY

This document summarizes a review of pregnancy exposure data reported to FDA in women treated with isotretinoin. The goal of this review was to compare isotretinoin pregnancy exposure data during the year prior to the implementation of the enhanced Isotretinoin Risk Management Program (Pre-RMP) to the first year of implementation of the enhanced RMP (Post-RMP).

It is important to keep in mind that the data for these analyses are primarily based on spontaneous reporting to passive surveillance systems such as AERS and are subject to reporting bias. It is possible for instance, that there was an increase in the reporting of pregnancies in the Post-RMP year, due to publicity around the implementation of the RMP. Additionally spontaneous reports are variable in quality and completeness; as such, lack of information does not necessarily indicate lack of compliance with the RMP. Furthermore, experience of pregnancy failures may not represent general experience of isotretinoin users.

The review of the pregnancy exposure data comparing the Pre-RMP to the Post-RMP period can be summarized as follows:

- One hundred twenty-seven (127) pregnancy exposures occurred during the Pre-RMP year and 120 cases occurred during the Post-RMP year. These numbers do not reflect an appreciable decrease in pregnancies with the enhanced RMP and may in fact reflect an increase relative to the overall decline in use of isotretinoin in the year following the implementation of the RMP.¹
- The number of women who were already pregnant prior to initiating therapy with isotretinoin is small and declined during the Post-RMP period relative to the Pre-RMP period (Pre-RMP-12, Post-RMP-7).
- Pregnancies occurred throughout isotretinoin treatment for both Pre-RMP and Post-RMP periods. Although more pregnancies occurred during the first month of isotretinoin use compared to other months (~15-19%), the aggregate number of pregnancies that occurred after the first month of isotretinoin therapy was greater than in the first month (~42-53%).
- The number of days of exposure to isotretinoin following conception has not changed between the Pre-RMP or Post-RMP periods.
- There has been no improvement in baseline pregnancy testing (49.6% and 50% for Pre-RMP and Post-RMP, respectively) and only a slight improvement in monthly pregnancy testing (35.4% and 39.1% for Pre-RMP and Post-RMP, respectively) and in the use of at least one method of birth control (53.5% and 58.3% for Pre-RMP and Post-RMP, respectively) among patients who became pregnant during the Pre-RMP period versus the Post-RMP period.

Although the actual reason that the pregnancies occurred could not be delineated from the cases in the series, some common themes were identified and could account for the pregnancy failures. These are summarized below:

- Twenty-one women were not using any form of contraception when the exposed pregnancy occurred or chose abstinence as a means of contraception and then went on to engage in unprotected sexual intercourse.
- Only 15% of women reporting birth control information reported use of “appropriate” birth control consisting of two methods, at least one of which was a primary method.
- Thirty-eight percent (38%) of women who reported using at least one form of contraception reported non-compliance with their chosen method of contraception. Non-compliant women either discontinued use of birth control early, missed doses of their oral contraceptive, or used contraception inconsistently.
- An evaluation of isotretinoin treatment start dates in relation to first day of the last menstrual period (LMP) and baseline pregnancy testing among 16 of 20 patients who were pregnant prior to initiating therapy with isotretinoin was performed.
 - Only two reported a baseline pregnancy test during the LMP.
 - None of the 16 patients started isotretinoin within two weeks of their LMP. Although the label does not instruct to start within a specified period of time around the LMP, it does state that the baseline pregnancy test should be conducted during the first five days of menses immediately preceding isotretinoin therapy, and that the prescription for isotretinoin should be dispensed within 7 days of the “qualification date” or confirmatory pregnancy test

¹ See Isotretinoin Utilization Review, pg 30.

- Seven women took isotretinoin without medical supervision. In five, the patients saved isotretinoin and restarted for an acne flare, one obtained isotretinoin at a swap meet, and one obtained a prescription in January but did not take until December of the same year.

The outcome of the pregnancy is unknown in almost half of all the pregnancy cases reviewed. As would be expected, this percentage is higher in the Post-RMP cases where outcomes may not yet have occurred or been reported. Sixty-seven percent (113/160) of those that reported pregnancy outcome information elected to terminate the pregnancy. Twenty-nine women delivered a live born infant and a small number of these cases reported a congenital anomaly.

In summary, the number of pregnancy exposures has not decreased appreciably and may have increased relative to the overall decrease in use of isotretinoin in the year following the implementation of the enhanced Isotretinoin Risk Management Program. Our review of a number of parameters comparing the Pre-RMP to the Post-RMP suggest minimal or no improvement with the implementation of the RMP. However, it should be emphasized that pre-specified pregnancy exposure metrics were not defined and that the experience of pregnancy failures may not represent general experience of isotretinoin users.

METHODS

All pregnancy cases submitted to the Agency after April 1, 2001 from the following sources were reviewed²:

- Reported directly to isotretinoin manufacturers (Roche, Genpharm (Mylan distributor), and Barr)
- Reported to the manufacturers via the isotretinoin patient surveys (Slone and SI Degge)
- Reports in the Adverse Event Reporting System (AERS)

Inclusion Criteria

Cases were included if they met the following criteria:

- Maternal fetal exposure to isotretinoin
- Isotretinoin administered orally
- Fetal exposure occurred during isotretinoin's use, or
- ≤ 30 days after isotretinoin discontinuation
- Estimated conception occurred during the following RMP phases (categories):
 - **Pre-RMP:** conception occurred between 4/1/01 to 3/31/02, including cases received by Roche, FDA, SI, Slone, generics by 8/15/02
 - **Post-RMP:** conception occurred between 4/1/02 to 3/31/03, including cases received by Roche, FDA, SI, Slone, generics by 8/15/03
 - **Unknown:** Conception date could not be determined but case was received from April 1, 2001 to August 15, 2003.

² Source: Adverse Event Reporting System, Request for Information – Roche Submission: September 18, 2003, Ranbaxy Submission: November 18, 2003, and Genpharm Submission: November 17, 2003.

RESULTS

Eight hundred and eight (808) cases from all sources were reviewed. Four hundred eighty-three cases were excluded for the following reasons:

- Conception occurred prior to April 1, 2001 – 255
- Conception occurred after March 31, 2003 – 36
- Paternal-fetal exposures – 35
- Conception occurred more than 30 days following discontinuation of isotretinoin – 78
- Conception occurred during the Pre-RMP period but was received after August 15, 2002 – 40
- Conception occurred during the Post-RMP period but was received after August 15, 2003 – 1
- Conception occurred an unknown period following isotretinoin discontinuation – 11
- Non-pregnancy related cases – 9
- Pregnancy in mothers exposed to isotretinoin by touch – 2
- Duplicate case – 15
- No patient identified – 1

1. GENERAL SUMMARY INFORMATION

Three hundred twenty-five pregnancy exposures from all sources met the inclusion criteria. The following table provides general information about the pregnancy exposures.

	Pre-RMP	Post-RMP	Unknown
Number of pregnancy exposures	127	120	78
During isotretinoin	95 (74.8%)	87 (72.5%)	67 (85.9%)
Within 30 days after isotretinoin	31 (24.4%)	31 (25.8%)	7 (9%)
Indeterminate	1 (0.8%)	2 (1.7%)	4 (5.1%)
Trimester exposed			
First	123	112	28
First and second	1	0	0
Unknown	3	8	50
Age (years)	n=111	n=101	n=27
Mean	22.7	24.1	25
Median	24	23	24
Range	14-36	14-42	15-50

One hundred twenty-seven cases were determined to have occurred during the year prior to the implementation of the enhanced RMP (Pre-RMP). One hundred twenty cases were determined to have occurred during the first year of implementation of the enhanced RMP (Post-RMP). Seventy-eight cases could not be categorized because the conception date was not reported and could not be estimated. The majority of the pregnancy exposures in all three categories occurred during the use of isotretinoin and during the first trimester of pregnancy. There was no difference in the median age of the women among all three categories.

1.1 Pregnancy Exposures by Report Source

Table 2 shows the pregnancy cases by report source. Pregnancy cases are voluntarily reported either directly to the manufacturers or to the FDA. They may also be reported via the Isotretinoin Patient Surveys.

Source	Pre-RMP	Post-RMP	Unknown Conception Date	Total
Slone	25	20	0	45
SI/Degge	0	12	6	18
Total Isotretinoin Survey	25	32	6	63
Direct to Manufacturer	99	86	72	257
Direct to FDA	3	2	0	5
Total Cases	127	120	78	325

- The majority of Pre-RMP and Post-RMP cases were reported directly to the manufacturer.
- Twenty percent (25/127) of the Pre-RMP cases and 27% (32/120) of the Post-RMP cases were reported by the isotretinoin patient survey conducted by the Slone Epidemiology Unit, and/or Degge/SI.

We attempted to determine whether any particular source provided more complete and better quality data (e.g. isotretinoin survey versus directly to manufacturer). Table 3 shows the number of data elements completed in the pregnancy exposure reports, stratified by source of the report.

Source	Pre-RMP (n=127)	Post-RMP (n=120)	Unknown (n=78)	Overall
Total Isotretinoin Survey	Range: 6 to 11, median=8 (n=5)	Range: 3 to 11, median 7 (n=32)	Range: 3 to 6, median=4 (n=6)	Range: 3 to 11, median=7 (n=63)
Direct to Manufacturer	Range: 1 to 11, median=6 (n=99)	Range: 1 to 11, median=6 (n= 86)	Range: 0 to 6, median=1 (n=72)	Range: 0 to 11, median=5 (n=257)
Direct to FDA	Range: 3 to 5, median= 4 (n=3)	Range: 3 to 9, median=6 (n=2)	-----	Range: 3 to 9, median=4 (n=5)

The data elements that were assessed included:

- Any baseline pregnancy information
- Any contraceptive information
- Any contraceptive compliance information
- The mother's age

- Any pregnancy testing during treatment information
- The last menstrual period date
- Isotretinoin therapy dates
- Estimated conception date
- Gestational age of the fetus
- Pregnancy outcome information
- Fetal outcome information

Overall, reports submitted by the patient surveys contained more data elements (median = 7) than reports submitted either by the manufacturer (median = 5), or reports submitted directly to the FDA (median = 4). It is not clear whether greater attempts for follow-up information occur in those pregnancy cases reported to the patient surveys.

It is important to note that the data elements assessed in these reports do not directly measure compliance with Isotretinoin Risk Management Program parameters as listed in the Hoffmann-La Roche, *1 Year Report on the S.M.A.R.T. Program*³ which include the following:

- Signed General Informed Consent
- Signed Female Informed Consent
- Received Spiral Notebook
- Received Instruction for Accutane Survey
- Enrolled in Accutane Survey
- Two Baseline Pregnancy Tests
- Monthly Follow-up Pregnancy Tests
- Yellow Sticker Attached to Rx
- Used two forms of contraception

1.2 Pregnancy Cases by Quarter

Cases by the conception date quarter for both Pre-RMP and Post-RMP cases were examined. Analysis of the number of pregnancies by quarter for the Post-RMP year was performed to determine whether there has been a decline in the number of cases over time after the implementation of the RMP (Table 4). In addition a comparison of each Post-RMP quarter relative to the same Pre-RMP quarter was made (Table 5).

	Pregnancies (% of total)
Quarter 1	26 (22%)
Quarter 2	29 (24%)
Quarter 3	19 (16%)
Quarter 4	19 (16%)
Unknown*	27 (23%)

*actual quarter conception occurred could not be determined in all Post-RMP cases

There were fewer cases reported during the last two quarters of the Post-RMP period compared to the first two quarters. It's not clear whether this decrease is due to improved compliance with the enhanced RMP over time, less follow-up time compared to earlier quarter, and/or whether this decline will continue into the second year following implementation of the RMP.

	Quarter 1 (Apr 1 – Jun 30)	Quarter 2 (Jul 1 – Sep 30)	Quarter 3 (Oct 1 – Dec 31)	Quarter 4 (Jan 1 – Mar 31)
Pre-RMP (n = 110)*	37	27	18	28
Post-RMP (n = 93)*	26	29	19	19
Percent Change from Pre-RMP to Post-RMP	- 30%	+ 7%	+ 5.5%	- 32%

*actual quarter conception occurred could not be determined in all Pre-RMP and Post-RMP cases

When each Post-RMP quarter was compared to the same Pre-RMP quarter, variations in all examined quarters were found. Variations between the quarters ranged from increased reporting of pregnancies by 7% in the second quarter to decreased reporting by 32% in the fourth quarter. The variations between quarters were not necessarily reflected by the change in use patterns over that same time frame (Table 6). Please see the Drug Utilization Review⁴ for more comprehensive isotretinoin usage information.

	Quarter 1 (Apr 1 – Jun 30)	Quarter 2 (Jul 1 – Sep 30)	Quarter 3 (Oct 1 – Dec 31)	Quarter 4 (Jan 1 – Mar 31)
Pre-RMP	377	338	394	398
Post-RMP	295	248	293	325
Percent Change from Pre-RMP to Post-RMP	- 22%	- 27%	- 26%	- 18%

US Data Source: IMS Health, IMS National Prescription Audit Plus™; for 4/01 to 3/03; accessed November 7, 2003.

1.3 Estimated Timing of Conception

The following table shows the estimated timing of conception relative to the isotretinoin treatment course. This was based on the most recent treatment course around the pregnancy.

Treatment Month	Pre-RMP (n=95)	Post-RMP (n=87)	Unknown (n=67)	All cases (n=249)
Prior to treatment**	12 (12.6%)	7 (8%)	1 (1.5%)	20 (8.0%)
During 1st month	18 (18.9%)	13 (14.9%)	1 (1.5%)	32 (12.9%)

⁴ See Isotretinoin Utilization Review, pg 30.

Treatment Month	Pre-RMP (n=95)	Post-RMP (n=87)	Unknown (n=67)	All cases (n=249)
During 2nd month	7 (7.3%)	7 (8 %)	0	14 (5.6%)
During 3rd month	7 (7.3%)	7 (8 %)	2 (3%)	16 (6.4%)
During 4th month	8 (8.4%)	15 (17.2%)	1 (1.5%)	23 (9.2%)
During 5th month	7 (7.3%)	5 (5.7%)	0	12 (4.8%)
During 6th month	8 (8.4%)	5 (5.7%)	0	13 (5.2%)
> 6 months	3 (3.1%)	7 (8 %)	1 (1.5%)	11(4.4%)
Indeterminate	25 (26.3%)	21 (24.1%)	61 (91%)	107 (43%)

*Based on isotretinoin start date to conception or positive pregnancy test; assuming a 30 day treatment period

** Percentage is based on the number of when who became pregnant during isotretinoin treatment; percentage is lower if applied to women who became pregnant during and within 30 days of discontinuation of isotretinoin.

For the 249 patients (of 325 total) that became pregnant during isotretinoin therapy, there were more reported pregnancies in the first month of isotretinoin therapy relative to subsequent individual months (15-19%); however the aggregate number of pregnancies that occurred after the first month of isotretinoin therapy was greater (~42-53%).

1.4 Days Exposure to Isotretinoin Following Conception

The following tables show the days of exposure to isotretinoin following conception. This is based on the estimated conception date to the day that isotretinoin was discontinued.

	Pre-RMP	Post-RMP	Unknown
Range	1 to 91 days	1 to 52 days	3 to 105 days
Mean	19.1 days	19.3 days	26.1 days
Median	17 days (n=71)	17 days (n=54)	14 days (n=8)

There was no difference in mean and median number of days exposed to isotretinoin following conception between the Pre-RMP and Post-RMP year. The following table shows these same data in ranges of days.

	Pre-RMP	Post-RMP	Unknown
<7 days	15 (15.7%)	11 (12.6%)	2 (3%)
7 to 14 days	18 (18.9%)	9 (10.3%)	2 (3%)
15 to 30 days	27 (28.4%)	21 (24.1%)	2 (3%)
> 30 days	11 (11.6%)	13 (14.9%)	2 (3%)
Number of days exposure unknown	24 (25.2%)	33 (38%)	59 (88%)
Total number during isotretinoin	95	87	67

The percentage of pregnant patients exposed to isotretinoin for greater than two weeks has not

changed from Pre-RMP to Post-RMP (40%; 38/95 and 39%; 34/87, for Pre-RMP and Post-RMP periods, respectively).

2. PREGNANCY TESTING

2.1 Baseline Pregnancy Testing Prior to Starting Isotretinoin

Two (urine or serum) baseline pregnancy tests, prior to starting isotretinoin therapy are mandated in the product label.

An evaluation of how often any baseline pregnancy testing was performed before starting isotretinoin therapy was performed. Any baseline pregnancy testing is defined as pregnancy testing occurring before starting isotretinoin therapy. Information on the type of pregnancy test (urine or serum) was inconsistently reported, therefore making it impossible to reliably determine the type of pregnancy test that occurred. A comparison of Pre-RMP data with Post-RMP data was made.

Table 10. Baseline Pregnancy Testing while using Isotretinoin		
	Pre-RMP n = 127	Post-RMP n = 120
Any Baseline Pregnancy Test	63 (49.6%)	60 (50%)
≥ 2 Baseline Tests	18	23
No Baseline Test Taken	4 (3.2%)	2 (1.7%)
Not Reported	60 (47.2%)	58 (48.3%)

Sixty-three (49.6%) Pre-RMP and 60 (50%) Post-RMP cases reported having at least one baseline pregnancy test before starting isotretinoin therapy. For those cases reporting baseline pregnancy testing, we found that slightly more than one-quarter (29%, 18/63) of the Pre-RMP cases, and more than one-third (38%, 23/60) of the Post-RMP cases reported at least two baseline pregnancy tests.

Four Pre-RMP cases (3.2%, 4/127) and two (1.7%, 2/120) Post-RMP cases reported having no baseline pregnancy testing performed and 60 (47.2%, 60/127) Pre-RMP and 58 (48.3%, 58/120) Post-RMP cases did not report whether or not baseline pregnancy testing had been performed.

2.2 Pregnancy Testing During Isotretinoin Therapy

The isotretinoin product label requires a pregnancy test each month prior to the female patient receiving an isotretinoin prescription.

An evaluation of compliance with pregnancy testing during isotretinoin treatment was performed. A comparison Pre-RMP data with Post-RMP data was made.

Table 11. Pregnancy Testing During Isotretinoin Therapy		
	Pre-RMP n = 127	Post-RMP n = 120
At Least One Pregnancy Test During Isotretinoin Therapy	45 (35.4%)	47 (39.1%)
No Pregnancy Test During Isotretinoin Therapy	4 (3.2%)	2 (1.7%)
Pregnancy Testing Not Reported	78 (61.4%)	71 (59.2%)

- Overall, 45 (35.4%) Pre-RMP cases and 47 (39.1%) Post-RMP cases reported at least one pregnancy test during isotretinoin use.
- Four (3.2%) Pre-RMP and 2 (1.7%) Post-RMP cases reported having no pregnancy testing during isotretinoin therapy.
- Additionally, 78 Pre-RMP (61.4%) cases and 71 (59.2%) Post-RMP cases did not report whether or not any pregnancy testing occurred during isotretinoin therapy. Of note 31 cases overall reported using isotretinoin for less than 30 days and may not have been eligible for pregnancy testing during treatment.

3. SUMMARY OF PATIENTS WHO BECAME PREGNANT PRIOR TO STARTING ISOTRETINOIN

3.1 Baseline Pregnancy Testing

A careful examination of the cases involving the 20 women who were pregnant prior to starting therapy with isotretinoin was performed. Sixteen of the 20 women reportedly received some pregnancy testing. The other four cases did not mention whether baseline pregnancy testing was conducted.

Of the 16 women who reportedly received baseline pregnancy testing, nine reported two or more baseline pregnancy tests, six reported “a” baseline pregnancy test, and the number of baseline tests was unknown in one case. The results of the pregnancy tests were negative in eight patients and positive in three. The results were unknown in the remaining five patients.

The following describe the circumstances of the three with positive pregnancy results:

- One patient had two negative tests at the doctor’s office and a subsequent home pregnancy test that was positive two weeks later and the day she initiated isotretinoin. She had taken only one dose (Post-RMP case).
- A 32 year old female had her LMP September 17. On October 23 a blood pregnancy test was performed. The following day she commenced isotretinoin but stopped after one pill when she found out she was pregnant (Pre-RMP case).
- A 33 year old female had her LMP June 3. She reportedly had irregular menstrual cycles. On July 26 a blood pregnancy test was performed. The following day she commenced isotretinoin. The pregnancy test was found to be positive, but according to the patient, was overlooked by the nurse. She had taken approximately 14 capsules and discontinued isotretinoin when another test was positive (Pre-RMP case).

3.2 Compliance with Label Recommendations

An evaluation of the isotretinoin treatment start date in relation to first day of the last menstrual period (LMP) and baseline pregnancy testing among patients who were pregnant prior to initiating therapy with isotretinoin was performed. The product label states that the second test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy. Sixteen of the 20 cases provided LMP dates.

Pre/Post RMP	LMP	BL Preg test date*	Isotretinoin start date	Days b/n BL Preg Test and isotretinoin start	Days b/n LMP and isotretinoin start
Pre	NR	Oct 1	Oct 1	0	Unable to determine
Pre	NR	Aug 10	Aug 10	0	Unable to determine
Pre	Jan 18	NR	Mar 5	Unable to determine	46
Pre	Feb 8	NR	Mar 15	Unable to determine	35
Pre	Mar 5	Feb 13	Feb 27	14	NA [§]
Pre	Mar 8	NR	Apr 1	Unable to determine	23
Pre	Apr 20	NR	Jul 27	Unable to determine	98
Pre	Jun 3	Jul 26	Jul 27	1	54
Pre	Jul 6	May 16	Jul 31	76	25
Pre	Aug 18	Aug 30	Sep 4	5	17
Pre	Aug 20	Sep 7	Sep 17	10	27
Pre	Sep 17	Oct 23	Oct 24	1	37
Post	NR	Dec 15	Dec 15	0	Unable to determine
Post	Jan 2	NR	Feb 3	Unable to determine	32
Post	Feb 4	in Jan	Feb 25	30+	21
Post	Feb 5	Feb 7	Feb 20	13	15
Post	Mar 28	NR	Apr 23	Unable to determine	26
Post	Sep 11	Sep 25	Sep 30	5	19
Post	Dec 24	Dec 29	Jan 15	17	22
Unk	NR	NR	NR	Unable to determine	Unable to determine

* Date is based on confirmatory or only baseline pregnancy test reported; in four women dates for the baseline pregnancy testing was not provided.

§ patient had menses during pregnancy

Only two reported a baseline pregnancy test during the LMP, both during the Post-RMP period. Seven of the 20 patients began isotretinoin therapy within 5 days of the baseline pregnancy test, however not in conjunction with the LMP. Moreover, none of the 16 patients (with an LMP date reported) started isotretinoin within two weeks of their LMP. Although the label does not instruct to start within a specified period of time around the LMP, it does state that the baseline pregnancy test should be conducted during the first five days of menses immediately preceding isotretinoin therapy, and that the prescription for isotretinoin should be dispensed within 7 days of the “qualification date” or confirmatory pregnancy test. It is perhaps the lack of specific instructions that may be a source of confusion to both practitioners as well as patients.

4. CONTRACEPTIVE USE

4.1 Contraceptive Use during Isotretinoin Therapy

Isotretinoin’s product label requires that female patients commit to two forms of effective birth control, at least one of which must be a primary form, unless absolute abstinence is chosen, or the patient has undergone a hysterectomy.

An evaluation of contraceptive use by patients reporting isotretinoin associated pregnancies was performed. A comparison of Pre-RMP data with Post-RMP data was made.

	Pre-RMP n = 127	Post-RMP n = 120
Any Birth Control Method	68 (53.5%)	70 (58.3%)
• One Method (any) (One Method - primary⁵)	50 (44)	61 (54)
• Two Methods (any) (Two methods – 1 primary)	18 (14)	9 (7)
No Birth Control Used/abstinence	15 (11.8%)	6 (5%)
Not Reported	44 (34.6%)	44 (36.7%)

The percentage of patients reporting any contraceptive use was about the same Pre-RMP and Post-RMP; however the percentage reporting no contraceptive use decreased during the Post-RMP year (11.8% and 5% for Pre-RMP and Post-RMP cases, respectively).

Of those reporting any contraceptive use, the following was noted:

- The majority of Pre-RMP cases (73.5%; 50/68) and Post-RMP cases (87.1%; 61/70) reported using one method of birth control during isotretinoin therapy.
 - When one method of birth control was used, the majority of both Pre-RMP (88%; 44/50) and Post-RMP (88.5%; 54/61) cases used a primary method of contraception.
 - A small number of Post-RMP cases (2/61) reported using the “morning after pill”.
- Of those cases reporting contraceptive use, 18 (26.5%) Pre-RMP cases, and nine (12.9%) Post-RMP cases reported using two methods of contraception.
 - When two methods were used by either group, the majority (Pre-RMP - 14, Post-RMP - 7) reported using at least one primary method of contraception.
 - A small number of Pre-RMP (4) and Post-RMP (2) cases used two secondary⁶ methods of contraception, instead of one primary and one secondary as described in the product label.
- Hormonal contraception (oral or injection) was the most common method of contraception used in the Pre-RMP (48) and Post-RMP (55) cases.

⁵ Primary methods of contraception: oral contraceptives, implantable hormones, injectable hormones, hormonal patch, intrauterine devices, hormonal vaginal contraceptive ring, sterilization (male, female)

⁶ Secondary methods of contraception: diaphragms, latex condoms, cervical cap,

Forty-four cases each (Pre-RMP 34.6%, Post-RMP 36.7%) did not report whether or not contraception was used during the time of isotretinoin use.

4.2 Contraceptive Compliance during Isotretinoin Therapy

Of the patients reporting contraceptive use, there were 32 Pre-RMP and 35 Post-RMP cases that provided information concerning contraceptive compliance during isotretinoin therapy. The majority of cases (82.1%; 23/28 Pre-RMP, and 80%; 28/35 Post-RMP) reported non-compliance with their chosen contraceptive methods. Five cases in each category reported contraceptive failure. There were two Post-RMP cases reporting both contraceptive failure and non-compliance.

	Pre-RMP	Post-RMP
Any Compliance Statement	28	35
Non-compliant	23	28
Contraceptive Failure	5	5
Contraceptive Failure <i>and</i> non-compliant	-----	2

Non-compliance refers to patients that discontinued use of contraceptive methods prior to label recommendations (during use and 30 days following isotretinoin discontinuation), or those that missed doses or otherwise inconsistently used contraceptive methods. Contraceptive failure is defined as those patients that reported “contraceptive failure”. Some examples of contraceptive failure included:

- Broken condoms
- Decreases in oral contraceptive effectiveness due to interacting medications (oral antibiotics, carbamazepine)
- Tubal ligation failure (procedure performed more than 10 years before estimated conception date)

5. OUTCOME DATA

Both pregnancy outcome and fetal outcome data for all 325 cases was tallied. Although these data are stratified by RMP period, any enhancements to the Isotretinoin RMP are unlikely to affect the pregnancy or fetal outcomes during these two periods.

5.1 Pregnancy Outcomes

The table below provides a summary of the pregnancy outcomes by RMP category.

	Pre-RMP (n=127)	Post-RMP (n=120)	Unknown (n=78)	Total (n=325)
Delivery	18	7	4	29
Spontaneous abortion/ectopic pregnancy	15	6	2	23
Elective Abortion	47	48	18	113
Unknown (lost to FU, pregnancy ongoing)	47 (37%)	59 (49%)	54 (69%)	160 (49%)

The outcome of the pregnancy is unknown in almost half of all pregnancy cases (160/325). As would be expected, this percentage is higher in the unknown and in the Post-RMP cases where outcomes may not yet have occurred been reported. About 35% of patients in the series elected to terminate their pregnancy. Nine percent (29/325) of patients delivered a live born infant.

The table below provides a breakdown of the 165 known pregnancy outcomes by time of isotretinoin exposure.

	Delivery	SAB/ectopic*	Elective Abortion
After discontinuation			
15 to 30 days	10	2	5
7 to 14 days	3	2	5
< 7 days	1	1	3
During isotretinoin			
< 7 days	5	4	5
7 to 14 days	4	3	14
15 to 30 days	2	2	29
> 30 days	1	5	11
Number of days exposed unknown	3	4	41
Total	29	23	113

*Spontaneous abortion and ectopic pregnancies

It appears that the longer the patient was exposed to isotretinoin following conception, the greater the tendency of the patient to terminate the pregnancy.

5.2 Fetal Outcomes

Twenty-nine patients reported delivery of a liveborn infant. Twenty reported normal babies (at time of reporting) of which four were born prematurely (2 to 5 weeks). Another mother had premature labor that was successfully stopped. In another case a mother with a history of epilepsy experienced seizure activity during pregnancy. Her pregnancy was further complicated by polyhydramnios, cord entanglement, small subchorionic hemorrhage, and decreased fetal movement but she subsequently delivered a normal baby. There was also another infant in whom a septal defect was noted in utero. Following birth, the infant underwent echocardiography which ruled out a defect.

Seven reported some type of abnormality and the fetal outcome in the remaining two was unknown. The mothers in three of the seven infants with an abnormality discontinued isotretinoin 15 to 25 days prior to conceiving. One infant developed gastroschisis and undescended testicles both events that required surgery. The other was a male infant who developed bilateral hydrocele and moulding of the anterior fontanel. In the third, an ultrasound in utero showed a small spot on the fetal heart. The mother delivered a female infant but no follow-up regarding a possible cardiac anomaly was provided.

The mothers in the remaining four infants that developed an abnormality conceived during isotretinoin therapy. Anomalies of the heart were reported in two cases, kidney in one case, and facial anomalies and retardation in one case. All four cases are briefly summarized below.

- A male infant was born with hypoplastic left heart syndrome. His mother had taken isotretinoin for Darier's disease and was on her third month of isotretinoin when she conceived and reportedly used contraception inconsistently (oral contraceptives and condoms). She discontinued isotretinoin about two weeks after conception. The infant underwent open heart surgery and was eventually discharged from the hospital. (PostRMP case)
- A female patient discontinued isotretinoin and her oral contraceptive about 3 weeks prior to conception, however took a single 40mg dose about 12 days after conception. An ultrasound examination at approximately 20 weeks gestation showed an atrial septal defect but normal valve movement over the foramen ovale. The mother gave birth to a female infant that was felt by the physician to be healthy. No additional followup information regarding the possible atrial septal defect was provided. (PreRMP case)
- A female patient discontinued treatment with isotretinoin about a month after conception. According to the reporter, the female patient had been on isotretinoin for over two years and had not undergone any pregnancy or other laboratory tests while receiving isotretinoin. Her pregnancy was complicated by premature contractions at 29 weeks and polyhydramnios. She delivered a male infant at 38 weeks with hydronephrosis. The infant was evaluated by a urologist who stated that a scan showed bilateral megaureters that were non-refluxing and did not appear to be obstructed. Renal function was 64% on the left and 36% of the right with sluggish drainage. The plan at the time of consultation was follow-up with repeat renal scan. (PreRMP case)
- This case was reported by a journalist who describes a female patient who became pregnant during the use of isotretinoin and subsequently delivered a baby with facial anomalies and retardation. It was not clear exactly when or how long the exposure to isotretinoin had occurred. (Unknown case)

The patterns of isotretinoin embryopathy are characteristic malformations involving craniofacial, cardiac, thymic, and central nervous system structures. The malformations include microtia/anotia, micrognathia, cleft palate, conotruncal heart defects and aortic-arch abnormalities, thymic defects, retinal or optic-nerve abnormalities, and central nervous system

malformations.⁷ Cognitive deficits in more than half the children exposed in utero have also been reported in follow-up studies to 5 years of age.⁸

DISCUSSION

The data for these analyses are primarily based on spontaneous reporting to passive surveillance systems such as AERS and are subject to reporting bias. It is possible for instance, that there was an increase in the reporting of pregnancies in the Post-RMP year, due to publicity around the implementation of the RMP. Additionally spontaneous reports are variable in quality and completeness; as such, lack of information does not necessarily indicate lack of compliance with the RMP. Furthermore, experience of pregnancy failures may not represent general experience of isotretinoin users.

Although there were no prespecified metrics agreed upon regarding any of these data, experience from pregnancy failures may help guide future RMP efforts to further reduce pregnancy exposures.

Review of the pregnancy exposure data comparing the Pre-RMP to the Post-RMP period can be summarized as follows:

- One hundred twenty-seven (127) pregnancy exposures occurred during the Pre-RMP year and 120 cases occurred during the Post-RMP year. These numbers do not reflect an appreciable decrease in pregnancies with the enhanced RMP and may in fact reflect an increase relative to the overall decline in use of isotretinoin in the year following the implementation of the RMP.
- The number of women who were already pregnant prior to initiating therapy with isotretinoin were 12 Pre-RMP and 7 Post-RMP.
- Pregnancies occurred throughout isotretinoin treatment for both Pre-RMP and Post-RMP periods. Although more pregnancies occurred during the first month of isotretinoin use compared to most other months (15-19%), the aggregate number of pregnancies that occurred after the first month of isotretinoin therapy was greater (~42-53%).
- The number of days of exposure to isotretinoin following conception has not changed between the Pre-RMP or Post-RMP periods.
- There has been no improvement in baseline pregnancy testing (49.6% and 50% for Pre-RMP and Post-RMP, respectively) and only a slight improvement in monthly pregnancy testing (35.4% and 39.1% for Pre-RMP and Post-RMP, respectively) and in the use of at least one method of birth control (53.5% and 58.3% for Pre-RMP and Post-RMP, respectively) among patients who became pregnant during the Pre-RMP period versus the Post-RMP period.

7 Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Broun JT, et al. Retinoic acid embryopathy. *N Engl J Med* 1985; 313:837-41.

8 Teratology Society. Recommendations for isotretinoin use in women of childbearing potential. *Teratology* 1991;44:1-6.

Although the actual reason that the pregnancies occurred could not be delineated from the cases in the series, some common themes were identified and could account for the pregnancy failures. These are summarized below:

- Twenty-one women were not using any form of contraception when the exposed pregnancy occurred or chose abstinence as a means of contraception and then went on to engage in unprotected sexual intercourse.
- The majority of women describe using only one method of birth control. Only 15% of women reporting birth control information reported use of “appropriate” birth control consisting of two methods, at least one of which was a primary method.
- Fifty-one of 138 women (38%) who reported using at least one form of contraception reported non-compliance with their chosen method of contraception. Non-compliant women either discontinued use of contraception early, missed doses of their oral contraceptive, or used contraception inconsistently.
- An evaluation of isotretinoin treatment start dates in relation to first day of the last menstrual period (LMP) and baseline pregnancy testing among 16 of 20 patients who were pregnant prior to initiating therapy with isotretinoin was performed.
 - Only two reported a baseline pregnancy test during the LMP.
 - None of the 16 patients started isotretinoin within two weeks of their LMP. Although the label does not instruct to start within a specified period of time around the LMP, it does state that the baseline pregnancy test should be conducted during the first five days of menses immediately preceding isotretinoin therapy, and that the prescription for isotretinoin should be dispensed within 7 days of the “qualification date” or confirmatory pregnancy test
- Seven women took isotretinoin without medical supervision. In five, the patients saved isotretinoin and restarted for an acne flare, one obtained isotretinoin at a swap meet, and one obtained a prescription in January but did not take until December of the same year.

The outcome of the pregnancy is unknown in almost half of all the pregnancy cases reviewed. As would be expected, this percentage is higher in the Post-RMP cases where outcomes may not yet have occurred or been reported. Sixty-seven percent (113/160) of those that reported pregnancy outcome information elected to terminate the pregnancy. Nine percent (29/325) of patients delivered a live born infant and a small number of these cases reported a congenital anomaly.

CONCLUSION

The number of pregnancy exposures has not decreased appreciably and may have increased relative to the overall decrease in use of isotretinoin in the year following the implementation of the enhanced Isotretinoin Risk Management Program. Our review of a number of parameters comparing the Pre-RMP to the Post-RMP suggest minimal or no improvement with the implementation of the RMP. However, it should be emphasized that pre-specified metrics were not defined and that experience of pregnancy failures may not represent general experience of isotretinoin users.