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Feb. 19, 1991

NOTE

TO: Jim Bilstad

From: Bob Nelson BC Nelson

Subj: Update on Accutane Activities

This interim briefing note is intended as an individual communication from the Chairman of the AMG to the ODE II Director. It is premature to consider the positions stated within as the consensus opinion of the AMG.

Activities/Interactions:

The AMG has expanded its membership to eight and now includes Wiley Chambers, the new responsible DAIDP group leader, and Franz Rosa the teratologist from DES. The Group has met with Roche on the following occasions to discuss the quarterly reports and to coordinate activities:

- September 18, 1990
- November 16, 1990
- December 13, 1990

The next AMG <-> Roche meeting is scheduled for February 21, 1991 (1:30 - 3:30pm in Room 13-B-39) to discuss the submission that arrived last week. That submission contained ADR, drug use, and Slone data through the end of 1990. These will be the data that will eventually go to the Advisory Committees. One or two "special epidemiology" meetings (see details below) are in the process of being scheduled. (the first one on NHANES has just been scheduled for Feb.21 9am)

At the Sept.18th meeting, the AMG presented a list of questions to Roche in an attempt to identify their positions and on which data-based issues (sources and estimates) we agreed upon and which there remained differences. (list is attached)

We also agreed that the exchange of information between the AMG and Roche would be more open and two-way. All parties (esp. Roche) felt that there were too many surprises and too much "data bickering" at the May '90 Advisory Committee Meeting.

At our Dec.'90 "special epidemiology" meeting with Roche & their consultants, Bruce Stadel (now Acting DES Director) announced a set of new DES strategies and efforts. Wiley & I have worked hard to

hold DES to the established timeframes. Additional special epidemiology meetings with Roche have been agreed to, and may be convened around the 2/21 AMG meeting. Most notably, Roche (via Harvard dermatologist/epidemiologist, Bob Stern) has performed a reanalysis of the NHANES data and has come up with estimates of the disease incidence that are very very different from the earlier DES estimates. We have brought Bob O'Neill and a NCHS expert in to assist us. I plan this as a topic of one of the special epi sessions. I'll keep you posted.

1991 Advisory Committee Meeting:

The AMG established March 7th as the submission deadline for both Roche and DES to submit their reports for the planned joint advisory committee meeting. As of today, it remains unscheduled --- Wiley has the lead and is trying to firm up the a date in May or early June.

Advisory Committee Questions --- Wiley, Bruce & I are meeting to discuss strategies and we will be contacting you shortly. Recall, that last year there were a variety of opinions on the depth and breadth of the questions and that the final decisions were made the day before the advisory committee meeting.

Data:

DRUG USE - The PDS-Beta data source was considered the best estimator of drug use in females. However, it was agreed that the best is only moderately good given its variance. Drug use data is important here for two reasons: 1] as an indicator of use incidence for comparison to disease incidence, and 2] as the sampling frame for the Slone study data (i.e., to understand the % enrolled, and thereby the rigor of the survey data)

Overall, no substantial decrease in Accutane use has occurred in the population at risk. It remains at the 55-65K per annum.

The database variance becomes a larger problem when attempting to estimate the % enrollment into the Slone study. These C.I. estimates yield a % enrollment of ~45-65% The higher figure could, debatedly, be considered high enough to be solidly interpretable. But given that the lower bound & the point estimate are not, we are in a limbo.

Bob O'neill and Yee Tsong of Biometrics are exploring the statistical assumptions that underlie the data extrapolation.

ADR Reports- Surprisingly, this is the area that I'm most excited about. I have always maintained that "defect baby counts" over time was a data bit of high emotional but little-to-no scientific value, especially given the possible increases in the proportion of induced abortions post-intervention. In my opinion, that slippery-slope was just uninterpretable.

However, Dr. W. Dai of Roche has done a content analysis of the defect cases that I feel is very valuable. Overall there are 1639 case reports of defective babies. Most defects have been reported retrospectively. However, a series of 332 reports were prospectively ascertained as pregnancy exposures, then followed to birth outcome. From these, 89 exposed pregnancies that were carried to term with the outcome distribution as follows: 25 (28%) were malformed, 7% low birth weight, 65% normal (her table 8a is also attached). More about this 28% defect rate in my discussion section.

SLONE - The vast majority of the females enrolled in this survey are still via the self-enrollment forms on the medication packages. Physician direct enrollment remains very low. Given the different enrollment rates/time the AMG asked that Slone's tables reflect a data cohort (i.e., most analizable data come fron the early cohort that had a estimated 27% enrollment rate) vs. the current cohort (which has an enrollment rate of up to 65% but only has the early data collected at present). More on this effort to follow.

DISCUSSION:

Unless Stern's NHANES reanalysis can convince DES, it still appears that the use of Accutane in females remains at levels that are orders of magnitude higher than the best estimates of the indicated disease incidence. The quantitative value of the submitted ADR reports approaches zero. The Slone study may yield some data of value but will require another year to obtain results from its highest enrolled cohort, and that may still be uninterpretable.

W.Dia's ADR content analysis provides new and valuable data. It confirms earlier CDC/Lammer data that the risk of defect given critical exposure is around 1:3 or 4. The pre-1988 labelling suffered from lack of risk quantitation and implied rarity (i.e., 1:1000-10,000+). In stark contrast, the 1988 intervention labelling strongly implies a 100% defect rate. These new data demonstrate a 28% rate and confirm Lammer's ealier (less rigorous) estimates of 25%.

Data from a Roche marketing study illustrate that, as a result of the intervention, almost all dermatologists are now fully informed of this important adverse outcome relationship to Accutane. Most (95+%) all are counselling on birth control. Given this, total pregnancy exposures are probably not much greater than the average contraceptive failure rate of three percent (3%). ---so far the pregnancy rate in the Slone data is one-tenth that or 3 per 1000.

Please recall the wording in the current product labelling implies a defect rate of 100%, given exposure. If both the informed prescriber and therefore, the patient believe that the defect rate is near 100%, it is reasonable to deduce that a vast majority of Accutane pregnancy exposures end with an abortion. That, of course directly mitigates most of the birth defect problem!

However, there are those anti-abortion advocates that argue for the pregnancy exposure itself to be the adverse outcome of consequence. I don't believe that that is realistic. On the other hand, pro-choice advocates consider this a "womens rights issue" . I also don't believe that currently this position realistic, because women aren't truly making an informed choice.

An informed choice can only be made in the presence of a data-based set of information as to the potential for risk. Such data should be transmitted to the patient through her physician once obtained from an accurate product label. Dr. Dai's new analyses gives us that data.

I continue to believe that near-zero risk can only be obtained through an appropriately designed and conducted restricted distribution system. I refer you to the documents that the AMG prepared last year on this subject. However, if a policy decision is made to accept a greater degree of overall risk then I suggest that a reasonable position for FDA/CDER to take is to have Roche modify the Accutane label (and pregnancy prevention package materials) and launch an immediate advertisement program to alert prescribers of the new best data on the probability of defects, given exposure.

With the exception of the individuals that are totally careless and those using diverted drug, I believe that this approach provides an informed ethical, though not absolute, solution to those females who elect to use this teratogen.

ATTACHMENTS:

--AMG questions to Roche
--Dr. Dai's 8A table

Table 8(a) ISOTRETINOIN-EXPOSED PREGNANCY REPORTS IN THE U.S. BY DURATION OF ESTIMATED FETAL EXPOSURE TO ISOTRETINOIN AND PREGNANCY OUTCOME

PROSPECTIVE CASES

Duration of Fetal Exposure (weeks)	Normal		Congenital Malformation		Spontaneous/ Missed Abortion		Abnormal Birth		Elective Abortion	
	No.	%	No.	%	No.	%	No.	%	No.	%
≤1	15	25.9	4	17.4	2	10.0	1	16.7	25	19.8
>1 to 2	6	10.3	6	26.1	5	25.0	1	16.7	15	11.9
>2 to 3	16	27.6	2	8.7	2	10.0	0	--	27	21.4
>3 to 4	9	15.5	2	8.7	4	20.0	1	16.7	23	18.3
>4 to 5	4	6.9	1	4.3	3	15.0	0	--	16	12.7
>5 to 6	1	1.7	1	4.3	3	15.0	0	--	7	5.6
>6 to 7	1	1.7	1	4.3	0	--	1	16.7	7	5.6
>7 to 8	0	--	1	4.3	1	5.0	1	16.7	5	4.0
>8	6	10.3	5	21.7	0	--	1	16.7	1	0.8
TOTAL	58	100	23	100	20	100	6	100	126	100

↓
updated to 25

2/19/91 not E
ATTACHMENT I

2/19/91 NOTE
ATTACHMENT II

DISCUSSION QUESTIONS REGARDING ACCUTANE
SEPTEMBER 17, 1990

OVERALL

DRUG USE

1]
* BEST ESTIMATOR FOR THE NUMBER OF PRESCRIPTIONS
* BEST ESTIMATE OF THE NUMBER OF PRESCRIPTIONS

2]
* BEST ESTIMATOR FOR THE NUMBER OF NEW INCIDENT FEMALE USERS
* BEST ESTIMATE OF THE NUMBER OF NEW INCIDENT FEMALE USERS

3]
* BEST ESTIMATOR FOR THE NUMBER OF NEW INCIDENT FEMALE USERS TRENDED OVER TIME
* BEST ESTIMATE OF THE NUMBER OF NEW INCIDENT FEMALE USERS TRENDED OVER TIME

PREGNANCY EXPOSURE

4]
* BEST ESTIMATOR FOR THE FREQUENCY OF PREGNANCY EXPOSURES
* BEST ESTIMATE OF THE FREQUENCY OF PREGNANCY EXPOSURES

PREGNANCY OUTCOMES

5]
* BEST ESTIMATOR FOR THE OUTCOMES OF PREGNANCY EXPOSURES
* BEST ESTIMATE OF THE OUTCOMES OF PREGNANCY EXPOSURES

6]
* BEST ESTIMATOR FOR THE PERCENT OF PREGNANCY EXPOSURES THAT WOULD HAVE RESULTED IN A DEFECTIVE BABY **IF** NOT ELECTIVELY ABORTED
* BEST ESTIMATE OF THE PERCENT OF PREGNANCY EXPOSURES THAT WOULD HAVE RESULTED IN A DEFECTIVE BABY **IF** NOT ELECTIVELY ABORTED

7]
* BEST ESTIMATOR FOR THE DISTRIBUTION OF DEFECT SEVERITY **IF** NOT ELECTIVELY ABORTED
* BEST ESTIMATE OF THE DISTRIBUTION OF DEFECT SEVERITY **IF** NOT ELECTIVELY ABORTED

WE ALSO NEED TO ASSESS HOW VALID AND RELIABLE THESE "BEST" ESTIMATORS ARE !

PREGNANCY PREVENTION

8]
* WAVE 10 OF TRACKING STUDY INDICATES THAT LESS THAN 7 IN 10 DERMATOLOGIST USE THE PREGNANCY KIT. THAT'S A DECLINE FROM EARLIER WAVES. HOW CAN THIS BE HANDLED IN THE LONG TERM

DISEASE

9]
* BEST ESTIMATOR FOR DISEASE (AS PER INDICATION) INCIDENCE
* BEST ESTIMATE OF DISEASE (AS PER INDICATION) INCIDENCE

SLONE STUDY

10]
* IS THE MOST RECENT (JULY, AUGUST) ENROLLMENT RATE STILL AROUND 600/WEEK

11]
* WHAT IS THE CURRENT PERCENT ENROLLMENT IN THE STUDY

12]
* WHAT IS THE OVERALL PERCENT ENROLLMENT FOR THE DATA THAT ARE USED IN THE SUBMITTED ANALYSES

13]
* WHAT PERCENT ENROLLMENT WOULD BE NEEDED TO PROVIDE INTERPRETABLE RESULTS, GIVEN AN INABILITY TO EXTERNALLY VALIDATE THE REPRESENTATIVENESS

14]
* HOW DO YOU PLAN TO ASSESS PERCENT ENROLLMENT FROM HID DATA

15]
* HOW VALID IS THE 60% PREGNANCY TEST (LESS IF SERUM ONLY) RATE ESTIMATE

16]
* IS THERE ANY REASON NOT TO CONSIDER THE "DISTURBING" SLONE DATA, eg. PERCENT PREGNANCY TESTED, AS A "BEST CASE SCENARIO"

17]
* EXPLAIN WHY ~80% OF SRS PREGNANCY REPORTS IN 1990 WERE OTHER THAN THOSE ENROLLED IN THE SEU STUDY

18]

* WILL THE ANALYSES OF THE POSTAL ARM (M-2) AND THEIR COMPARISONS TO THE PHONE ARM BE AVAILABLE FOR THE NEXT FDA REPORT AND FOR THE OCT.26 SEU ADVISORY COMMITTEE

DATA REQUESTS FOR THE NEXT AMG REPORT

19]

* NEED FROM YOUR BEST ESTIMATOR, FREQUENCY DISTRIBUTIONS ON SEVERITY OF DISEASE (i.e., VIA NUMBER OF CYSTS, ESP. 5+, 10+, 15+ CYSTS), AS WELL AS BODY LOCATION OF THE CYSTS/SCARRING

20]

* NEED FROM YOUR BEST ESTIMATOR, PATHOLOGY AND EXPOSURE TIME DATA FOR THE SPONTANEOUS ABORTION, ELECTIVE ABORTION, AND BORN DEAD OUTCOME CATEGORIES; AS WELL AS, EXPOSURE TIME DATA FOR LIVE BIRTH, NORMAL AND DEFECTIVE.

21]

* NEED FROM YOUR BEST ESTIMATOR, DATA ON 1] PERCENTAGE OF ALL PREGNANCY EXPOSURES THAT COULD RESULT IN DEFECTS (i.e., DEFECT RATE), IF NOT ELECTIVELY ABORTED, 2] DISTRIBUTION OF DEFECT SEVERITY

22]

* COPIES OF MATERIALS THAT ARE MAILED TO CLINICIANS WHEN INQUIRING ABOUT PREGNANCY EXPOSURES

SUBSEQUENT MEETINGS

DEADLINE FOR ROCHE & DES REPORTS : ~~FEB~~ MARCH 7, 1991

AMG + ROCHE - FEB.21, 1991

JOINT ADVISORY COMMITTEE MEETING - ~~LATE MARCH~~ MAY or EARLY June