CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

OFFICE DIRECTOR MEMO

6/27/06

Division Director Memorandum

NDA:	21-864
Tradename:	Lybrel™
Indication:	Prevention of pregnancy in women who elect to use this product as a method of contraception
Dosage Form/Route:	Tablet/Oral
Drug/Dose:	90 µg levonorgestrel/ 20 µg ethinyl estradiol – daily continuous administration
Applicant:	Wyeth Pharmaceuticals, Inc.
Original Submission Date:	May 27, 2005
Supplemental Information Date:	March 13, 2006
PDUFA Goal Date:	June 27, 2006
Date of Memorandum:	June 26, 2006

1.0 Background and Regulatory History

With this application, Wyeth is seeking approval of a combination oral contraceptive product (Lybrel) with a dosing regimen that consists of daily continuous administration of levonorgestrel (LNG) and ethinyl estradiol (EE). The drug product proposed by Wyeth contains a lower dosage of the progestin drug component, LNG (90 µg), and the same dose of the estrogen drug component, EE (20 µg), as found in the approved drug product Alesse® (100 µg of LNG and 20 µg of EE).

There are currently two other extended cycle contraceptive products on the US market. They are Seasonale and Seasonique. The Seasonale regimen contains LNG 150 µg/EE 30 µg administered on days 1-84, followed by placebo on days 85-91 (hormone free period or HFP). The Seasonique regimen differs only in that the placebo is replaced with tablets containing 10µg of EE.

The original application for NDA 21-864 was submitted on May 25th, 2005. Additional clinical information was submitted on March 13, 2006. The March submission was a major amendment, resulting in an extension of the PDUA goal date to June 27, 2006.

Chemistry and Manufacturing issues remain unresolved. In addition, there are major disagreements regarding important clinical issues between the clinical review team and the Division Director. A discussion of these clinical issues follows.

2.0 Clinical Contents of 21-864

Two one-year, Phase 3, multicenter, open-labeled studies were submitted with the NDA to support the efficacy and safety of Lybrel™. They were Study 0858A2-313-NA (Canada and the US) and Study 0858A2-315-EU (Europe).

2.1 Study 313NA

This was a single-armed study that included healthy women aged 18-49 who were sexually active, at risk of becoming pregnant, and willing to rely upon the LNG 90 μg/EE 20μg continuous use product as their only method of contraception for the duration of the 13–cycle study. Subjects were enrolled from 80 sites in North America (Canada and the US). The study was conducted from February 2003 through September 2004. Two thousand four hundred and two (2,402) subjects were enrolled and 2,134 subjects took at least 1 dose of study drug. Of the 2,134 subjects who took at least 1 dose of study drug, 77% (1646 subjects) were Caucasian, 10.17% (217) were Black, 8.81% (188 subjects) were Hispanic, 1.55% (33 subjects) were Asian, and 0.23% (5 subjects) were identified as other. Forty-three percent (43%) had never been pregnant and 79% were non-smokers. The mean age was 28.8 years, and 1,762 subjects were 35 years of age or younger at the start of enrollment (population used for efficacy calculation). The mean weight and mean body mass index were 70.38 ±16.83 kg and 26.04±6.07 kg/m^2, respectively, in the enrolled population.

2.11 Contraceptive Efficacy

The primary endpoint, for the evaluation of oral contraceptives has traditionally been the Pearl index (PI). The Pearl index is defined as "pregnancies per 100 woman-years of use." It is computed by dividing the number of "on-treatment" pregnancies by the number of at-risk 28-day treatment cycles or pill packs distributed, and multiplying the value by 1300. The effectiveness of a contraceptive can be represented by the Pearl index (a proportion), and the 2-sided 95% confidence intervals (CI) of the point estimate.

The denominator of the Pearl index, for studies 313NA and 315 EU consisted of the number of 28-day treatment cycles taken by the study subjects except for those cycles during which:

1. Backup contraception was used (or unknown);
2. Three (3) or more consecutive days of pill were missed, either
   - During current pill pack, or
   - The missed consecutive days spanned the previous pill pack into the current pill pack, ending in current pill pack (current pill pack was to be excluded), or
   - What should have been the start of study drug of the first pill pack only if he subject started taking her first pill on day 4 or later from the start of her menses;
3. Five (5) or more total days of pills were missed in any pill pack;
4. Prohibited medication was taken within a time frame that could affect contraceptive efficacy;
5. The subject was not sexually active (or unknown); or
6. For subjects who became pregnant, any pill pack that began after the Estimated Date of conception (EDC).

For the studies in the submitted NDA, the "on-treatment" pregnancies (numerator of the PI) was defined as the number of pregnancies in which conception occurred between the start of the study drug through 14 days following the last dose of study drug. Generally the primary analysis for efficacy is the PI based on subjects 35 year old and under

population at entry. Women over 35 are primarily included for evaluation of safety. The inclusion of the over 35y/o women in the PI calculation will usually result in a lower PI because of the lower fecundity of this population.

The total number of on-treatment pregnancies in Study 313-NA was 23 (all in 35 y/o and under)
Using a total of 12,572 pill packs or 28-day treatment cycles (see table 1), the calculated PI for 313NA is **2.38 (95% CI 1.51, 3.57).**

Table 1

Number (%) of Pill Packs (i.e., 28-Day Cycles) Excluded from Pearl Index Analyses of Contraceptive Efficacy by Reason: Subjects Aged 35 years or Younger---Sponsor's Table 9.1.2-2

Reason	Number (%)
Pill packs included	12,572 (82)
Pill packs excluded[a]	2681 (18)
Backup contraception used (or unknown)	1393 (9)
Missed ≥ 3 consecutive pills	87 (< 1)
Missed ≥ 5 pills total in any 1 pill pack	106 (< 1)
Prohibited medication	222 (1)
Not sexually active (or unknown)	1008 (7)
Pregnant before pill pack start	16 (< 1)

a: A pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason for exclusion applied was excluded.

2.12 Discontinuations

Of 2,134 subjects who took one dose of the study drug, 921 (43.2%) completed the study. There were 1,213 (56.8%) subjects who discontinued for various reasons (table 2). Three-hundred and sixty three 363 (17%) subjects discontinued due to an adverse event (AE). Of these 363 subjects, 181, discontinued due to a bleeding related AE.

Another 336 (15.7%) of subjects discontinued due to subject request. According to the primary medical officer, a review of the case report forms revealed that many of these subjects were having bleeding problems, but not to an extent that it was listed and an AE.

Table 2

The Primary Reasons for Discontinuations Sponsor's Table 8.1.1-1

Reason	LNG 90 µg/EE 20 µg Continuous-Use Regimen
Total	2134 (100)
Completed	921 (43.2)
Discontinued[a]	1213 (56.8)
Accidental pregnancy	19 (0.9)
Adverse event[b]	363 (17.0)
Discontinuation of study by sponsor	102 (4.8)
Investigator request	11 (0.5)
Lost to follow-up	223 (10.4)
Planning pregnancy	19 (0.9)
Protocol violation	140 (6.6)
Subject request	336 (15.7)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.

a: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.

b: Total includes subject 313-091-8311, who did not have a specific event identified on the case report form. Adverse event was listed on the termination record for this subject but no event was specified and no adverse event was identified on the adverse event case report form as the reason for withdrawal.

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2.13 Cycle Control (analysis of patterns of intermenstrual bleeding, breakthrough bleeding, spotting, and the absence of withdrawal bleeding)

The sponsor used the following definitions for vaginal bleeding in the two studies:

- Bleeding: sanitary protection was required;
- Spotting: some bleeding but no sanitary protection was required; and
- Amenorrhea: no bleeding or spotting during the period of interest.

One of the reasons for the development of a continuous use oral contraceptive is that a subject could have sustained amenorrhea or at least significantly reduced vaginal bleeding in order that such bleeding would not interfere with her daily activities. In addition, some believe that by eliminating menses on a monthly basis the symptoms relating to hormone fluctuation during natural menses such as headache, cramping, bloating, emotional disorders could be lessened and thus improve a woman's quality of life.

Table 3 indicates the bleeding pattern of women in 313NA. At cycle 6, 555 (39.6%) of subjects remaining the trial were amenorrheic. By this time, the number of subjects in the trial has decreased from 2,134 to 1,403.

At cycle 13, 505 (58.7%) of subjects remaining were amenorrheic. At this point in the study, however, more than half of subjects were no longer in the study.

Table 3
Incidence of Amenorrhea and No Bleeding per Pill Pack (28-day cycle). Sponsor Table 9.4.2.2.1-1

Pill Pack	n	Amenorrhea [a] n (%)	No Bleeding (With or Without Spotting) n (%)
LNG 90 µg/EE 20 µg Continuous-Use Regimen			
1	2048	48 (2.3)	124 (6.1)
2	1947	450 (23.1)	936 (48.1)
3	1671	446 (26.7)	878 (52.5)
4	1545	502 (32.5)	927 (60.0)
5	1469	540 (36.8)	943 (64.2)
6	1403	555 (39.6)	929 (66.2)
7	1220	546 (44.8)	864 (70.8)
8	1173	600 (51.2)	891 (76.0)
9	1144	601 (52.5)	870 (76.0)
10	1070	584 (54.6)	841 (78.6)
11	1014	597 (58.9)	821 (81.0)
12	977	604 (61.8)	816 (83.5)
13	860	505 (58.7)	679 (79.0)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.
a: Amenorrhea = no bleeding or spotting.

2.2 Study 315EU

Study 0858A2-315-EU was a two-armed, open label comparative trial of the LNG 90 µg/EE 20µg continuous use regimen (Lybrel™) vs. a cyclic regimen of LNG 100 µg/EE 20µg for 21 days and placebo on days 22 to 28. The comparator is marketed in the European Union (EU) as Loette® and as Alesse® in the US. Healthy women aged 18-49 who were sexually active, at risk of becoming pregnant and willing to rely upon the study drug as their only method of contraception for the duration of the 13 x 28-day cycle study were eligible for enrollment. Subjects were enrolled from 44 sites in Europe. The study was conducted from March 2003 to October 2004.

Six hundred and fifty-one (651) subjects were randomized and 641 subjects took at least 1 dose of study drug (323 in the LNG 90 µg/EE 20µg continuous use regimen and 318 in LNG 100 µg/EE 20µg cyclic regimen). Of the 641 subjects, 96.4%/ (618) were Caucasian, 1.4% (9) were Black, 0.8% (5) were Asian and 1.4% (9) of subjects were identified as other. The mean age was 27.35 years. There were 544 subjects in the study population who were 35 years or younger at the time of enrollment. The mean weight and mean body mass index were 63.8 and 22.74 kg/m^2, respectively. Sixty-one percent (61%) had no prior pregnancies. Seventy and five tenths percent (70.5%) reported that they were non-smokers.

2.21 Contraceptive Efficacy

A total of 2,564 (89%) pill packs (28-day cycle equivalents) in the continuous-use regimen and 2,733 (88%) pill packs in the cyclic regimen were included in the Pearl index analyses for 544 subjects who were aged 35 years or younger at the beginning of

this study.

The number of pill packs excluded from the Pearl index calculation is summarized by treatment group and reason for exclusion in Table(4)

Table 4

Number of (%) of Pill Packs (28-day Cycle Equivalents) Excluded from the Pearl Index by Reason for Subjects Aged 35 Years or Younger at Start of Study. Sponsor's Table 9.1.2-1

	LNG 90 µg/EE 20 µg (n = 2881)	LNG 100 µg/EE 20 µg (n = 3116)
Total pill packs included	2564 (89)	2733 (88)
Total pill packs excluded[a]	317 (11)	383 (12)
Backup contraception used	107 (4)	204 (7)
Missed ≥ 3 consecutive pills	16 (< 1)	21 (< 1)
Missed ≥ 5 pills total in any pill pack	16 (< 1)	16 (< 1)
Prohibited medication	2 (< 1)	15 (< 1)
Not sexually active or unknown	195 (7)	158 (5)

a: A pill pack may have been excluded for more than 1 reason. Only the pill packs to which these criteria apply were excluded.

There was one pregnancy (including days 1-14 post treatment) in the continuous regimen (see table 5) in the 2564 28-day at risk treatment cycles. Therefore the calculated PI for the continuous regimen was **0.51 (0.01, 2.82).**

There were 3 pregnancies (see table 5) in the 2,733 28-day cycles among the cyclic regimen treated women which results in a PI of **1.43 (0.29, 4.17).**

Table 5

Summary of the Four Pregnancies in Study 315-EU. Sponsor's Table 9.4.2.1-1

Subject Number	Classification	Total Duration on Study Medication	Estimated Date of Conception (Relative Day)
	LNG 90 µg/EE 20 µg Continuous		
315-001-0013	Not classified[a]	364	Posttreatment (6 days)
	LNG 100 µg/EE 20 µg Cyclic		
315-026-1147	Method failure	245	211
315-034-2252	User failure	189	179
315-034-2247	User failure	294	289

a: Not classified for the Pearl Index. Subject was compliant with respect to taking study drug within 30 days of EDC (including the posttreatment portion of that 30 day period, when study drug was not taken), and was classified as a method failure for the life table.

2.22 Discontinuations

Overall, 176 (27%) of subjects discontinued from the study: 107 (33%) subjects in the continuous use treatment group and 69 (22%) in the 21-day cyclic regimen ($p<0.001$). The primary reasons for discontinuations are summarized in the following table (6)

Table 6

Number (%) of Subjects who Discontinued from the Study by Primary Reason. Sponsor Table 8.1.1-1

Reason	LNG 90 µg/EE 20 µg n = 323	LNG 100 µg/EE 20 µg n = 318	Overall p-Value[a]
Total[b]	107 (33.1)	69 (21.7)	0.001**
Accidental pregnancy[c]	0 (0.0)	3 (0.9)	0.122
Adverse event	72 (22.3)	31 (9.7)	<0.001***
Investigator request	1 (0.3)	2 (0.6)	0.621
Lost to follow-up	5 (1.5)	2 (0.6)	0.451
Planning pregnancy	3 (0.9)	3 (0.9)	1.000
Protocol violation	9 (2.8)	11 (3.5)	0.656
Subject request	17 (5.3)	17 (5.3)	1.000

a: p-Value obtained from the Fisher exact test (2-tail).

b: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.

c: One (1) accidental pregnancy in the LNG 90 mg/EE 20 mg group occurred with an EDC 6 days after the last dose of study drug and therefore, did not discontinue early from the study.

* Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

The difference between treatment groups in the total discontinuations rate is attributable to a difference in withdrawals because of adverse events ($p <0.001$). Adverse events are the most frequent reason for discontinuation of study drug.

Forty- seven (47) of 72 (65.2%) of the continuous group and 12 of 31 (38.7%) of the cyclic group reported adverse events related to bleeding disorders (menorrhagia, metrorrhagia, uterine hemorrhage and vaginal hemorrhage).

2.23 Cycle Control

The following tables (7A, 7B) report the bleeding patterns in the continuous and cyclic group for study 315EU.

Table 7A

Summary of Bleeding Pattern in Continuous Group by Pill Pack Number and Percentage of Subjects. Sponsor Table 9.4.2.2.1-1

			Total				
Pill Pack	n	Amenorrhea	Bleeding (With No Spotting)	Spotting (With No Bleeding)	Bleeding and/or Spotting	Bleeding (With or Without Spotting)	No Bleeding (With or Without Spotting)
LNG 90 µg/EE 20 µg Continuous							
1	317	14 (4.4%)	43 (13.6%)	14 (4.4%)	303 (95.6%)	289 (91.2%)	28 (8.8%)
2	307	100 (32.6%)	17 (5.5%)	70 (22.8%)	207 (67.4%)	137 (44.6%)	170 (55.4%)
3	292	79 (27.1%)	16 (5.5%)	68 (23.3%)	213 (72.9%)	145 (49.7%)	147 (50.3%)
4	281	87 (31.0%)	13 (4.6%)	80 (28.5%)	194 (69.0%)	114 (40.6%)	167 (59.4%)
5	271	103 (38.0%)	9 (3.3%)	70 (25.8%)	168 (62.0%)	98 (36.2%)	173 (63.8%)
6	264	97 (36.7%)	11 (4.2%)	71 (26.9%)	167 (63.3%)	96 (36.4%)	168 (63.6%)
7	240	95 (39.6%)	7 (2.9%)	70 (29.2%)	145 (60.4%)	75 (31.3%)	165 (68.8%)
8	236	117 (49.6%)	4 (1.7%)	57 (24.2%)	119 (50.4%)	62 (26.3%)	174 (73.7%)
9	228	119 (52.2%)	2 (0.9%)	54 (23.7%)	109 (47.8%)	55 (24.1%)	173 (75.9%)
10	226	118 (52.2%)	5 (2.2%)	51 (22.6%)	108 (47.8%)	57 (25.2%)	169 (74.8%)
11	222	115 (51.8%)	5 (2.3%)	55 (24.8%)	107 (48.2%)	52 (23.4%)	170 (76.6%)
12	220	124 (56.4%)	3 (1.4%)	54 (24.5%)	96 (43.6%)	42 (19.1%)	178 (80.9%)
13	210	111 (52.9%)	4 (1.9%)	55 (26.2%)	99 (47.1%)	44 (21.0%)	166 (79.0%)

In the continuous group, at cycle 6, 97 of 264 (36.7%) of the remaining subjects are amenorrheic. At cycle 13, 111of 210 (52.9%) of the remaining subjects are amenorrheic (table 7A)

Table 7B

Summary of Bleeding Pattern in Cyclic Group by Pill Pack Number and Percentage of Subjects. Sponsor Table 9.4.2.2.1-1

			Total				
Pill Pack	n	Amenorrhea	Bleeding (With No Spotting)	Spotting (With No Bleeding)	Bleeding and/or Spotting	Bleeding (With or Without Spotting)	No Bleeding (With or Without Spotting)
LNG 100 µg/EE 20 µg Cyclic							
1	308	0 (0.0%)	45 (14.6%)	4 (1.3%)	308 (100.0%)	304 (98.7%)	4 (1.3%)
2	296	3 (1.0%)	69 (23.3%)	8 (2.7%)	293 (99.0%)	285 (96.3%)	11 (3.7%)
3	290	2 (0.7%)	54 (18.6%)	11 (3.8%)	288 (99.3%)	277 (95.5%)	13 (4.5%)
4	292	4 (1.4%)	56 (19.2%)	16 (5.5%)	288 (98.6%)	272 (93.2%)	20 (6.8%)
5	284	1 (0.4%)	47 (16.5%)	15 (5.3%)	283 (99.6%)	268 (94.4%)	16 (5.6%)
6	281	2 (0.7%)	58 (20.6%)	6 (2.1%)	279 (99.3%)	273 (97.2%)	8 (2.8%)
7	267	6 (2.2%)	54 (20.2%)	10 (3.7%)	261 (97.8%)	251 (94.0%)	16 (6.0%)
8	266	3 (1.1%)	53 (19.9%)	17 (6.4%)	263 (98.9%)	246 (92.5%)	20 (7.5%)
9	262	5 (1.9%)	49 (18.7%)	17 (6.5%)	257 (98.1%)	240 (91.6%)	22 (8.4%)
10	254	1 (0.4%)	45 (17.7%)	8 (3.1%)	253 (99.6%)	245 (96.5%)	9 (3.5%)
11	255	4 (1.6%)	46 (18.0%)	6 (2.4%)	251 (98.4%)	245 (96.1%)	10 (3.9%)
12	255	5 (2.0%)	42 (16.5%)	10 (3.9%)	250 (98.0%)	240 (94.1%)	15 (5.9%)
13	229	3 (1.3%)	44 (19.2%)	23 (10.0%)	226 (98.7%)	203 (88.6%)	26 (11.4%)

Data for the 12 subjects with bleeding data at pill packs 14 and 15 are not shown.

Table 7B is included only to illustrate a typical bleeding pattern observed in a cyclic regimen.

3.0 Primary Medical Officer and Medical Team Leader Comments and Conclusions

This section (3.0) includes direct quotes and synopses of comments by the primary medical officer and medical team leader (referred to as the review team) for this product. I have attempted to fairly summarize their views of the salient issues as expressed in their respective reviews of Lybrel. The reader is referred to the memoranda of the review team for the complete representation of their arguments.

3.1 Contraceptive efficacy: The review team believes that historically it was accepted that effectiveness for combination oral contraceptive drug product would be established with demonstration of a Pearl Index (method +user failure) of less than 1. In 1975, the Division (HFD-510) took the issue of approval for Ovcon35 to the Reproductive Health Advisory Committee (AC). At issue was the ***high*** Pearl Index (**1.36**) of this combination oral contraceptive containing lower amounts of norethindrone (400 μg) and ethinyl estradiol (35 μg) compared to other conventional combination oral contraceptive products of that time. Following discussions at the AC, a cut-off for Pearl Index of 1.5 to establish effectiveness was adopted. Over the years as the doses of progestin and estrogen anticipated to suppress ovulation have been lowered, the Division-accepted cut-off value for the Pearl Index was allowed to rise to 2.

The review team further believes that during the earlier days of combined oral contraceptives when the drug products consisted of high doses of the estrogen and progestin components, the Division (HFD-510) determined that because there were so few method failure pregnancies that in order to have reasonably sized clinical trials, effectiveness would be determined by a failure rate (i.e. pregnancy rate) that considered both method and user failures. User failure rates were limited to patients who followed the protocol with minor violations (as in this protocol subjects who missed greater or equal to three consecutive pills or five in a single pill pack were discontinued and their cycles not counted). As the determination was made that oral contraceptives were safe to use into the perimenopausal years (up to age 50), it was decided that effectiveness should be determined not in all women (i.e. up to age 50), but in the sub-group of women who have higher fecundity and are thus at greater risk. Therefore, evaluation of effectiveness was limited to the population of women less than or equal to age 35.

As determined in the primary "proof of efficacy" study, Study 0858A2-313-NA, in women less than or equal to age 35, Lybrel™ has a Pearl Index (method plus user failure pregnancies) of 2.38 (95% CI 1.51, 3.57). The review team states that "When judged against the cut-off value for Pearl Index less than or equal to 2.0, the point estimate and 95% upper bound limit are clearly outside contemporarily used by the Division to determine effectiveness. In addition the high proportion of contraceptive failures that are a result of "method failures" is disturbing."

As far as efficacy, it is unclear to the review team, as to why there is a difference in the Pearl index between the US (PI 2.38) and European (PI 0.51) trials. Possible explanations are better patient compliance and lighter weight of the subjects in the European population.. It should also be noted that the European trial was less ethnically diverse. The primary reviewer states that "In conclusion, while the sample size of this small comparative study is *not large enough to assess pregnancy rates*, from an efficacy standpoint, it would appear that women who take Lybrel are not at a greater risk of pregnancy than Alesse."

The sponsor proposed an analysis that would have combined the results of the two trials with a resultant lower PI than in 313NA alone. This analysis was rejected by the review

team because neither the protocol nor the proposed meta-analysis and it's statistical plan was proposed by the sponsor a priori, the trial populations were different, and 315EU "was clearly under-powered in terms of a US contraceptive trial."

3.2 Discontinuations: The review team state and present data that indicate that the discontinuation rate from 313NA is the highest that they can find among contraceptive trials for 20 to 30 mcg pills. (table 8)

Table 8

Study Discontinuation Rates (%) for 20-30 mcg dose OCs

LN90 EE20	Alesse * LN 100/ 20EE	Lo-Estrin NET 100 20EE	Mircette DES0 150/EE20 10EE (days 2428)	Cyclessa DESO 100/125/150 EE25	Ortho TriCyclenLo NORGES 180/215/250 EE25	Nordette LN150 EE30	Seasonale LN150 EE30	YAZ 20DESO 20EE	Lo-Estrin/24* NETA100/ EE20
56.8	9.0	25.6	47.0	18.2	25.6	28.8	40.6	5.6	22

*6-month cycle trial, some of these discontinuation rates have been complied in more recent comparative trials used to supplement approval of lower dose COCs

The primary reviewer states that;

"The previous highest discontinuation rate presented in a clinical trial was that of Mircette® at 47.0%. Other products range between a low of 5.6% (Yaz®) to 25.6% for Loestrin® and Ortho TriCyclenLo®. All of these products contain 20-25mcg of EE. Note that the discontinuation rate of Lybrel™ is 56.8%."

3.3 Cycle Control: The review team has serious concerns regarding the lack of cycle control in the form of irregular bleeding and spotting in subjects using Lybrel. The medical team leader states that:

"It is difficult to assess the bleeding associated with one drug product relative to that demonstrated in a separate trial for another product. Various sponsors have utilized different measures to discuss bleeding. However, the extended and continuous cycle regimens would appear to have more unanticipated bleeding than the cyclic regimens which are designed to have an approximately 28-day withdrawal bleed. As stated at the outset of this Discussion section, in addition to providing effective contraception, this product was intended to provide sustained amenorrhea. In the study report for Study 0858A2-313-NA, the Sponsor states "*In addition to inhibition of menses, the LNG 90 µg/EE 20 µg continuous use regimen is intended to reduce all types of bleeding and spotting*".

The question is should a Sponsor who purports that their product provides sustained amenorrhea and reduces all types of bleeding and spotting be required to provide the evidence that demonstrate this? My response to this question is yes. The clinical trial data did not demonstrate sustained amenorrhea. At cycle one, 98% of subjects had bleeding and/or spotting. By cycle 13, 40% of subjects had bleeding and/or spotting. While one can say that the percentage of subjects with bleeding and/or spotting improved from cycle 1 to cycle 13, a product that demonstrates 40% of women to

have bleeding and/or spotting at one year certainly does not represent sustained amenorrhea or reduced bleeding and spotting.. Another concern to think about is whether with "real world" use, the poor cycle control might lead women to discontinue this drug product thereby increasing the exposure of these women to unintended pregnancies."

The medical team leader further states that:

"In this reviewer's opinion, the enormous public health impact of unintended pregnancies linked to discontinuations of oral contraceptives because of poor cycle control argues heavily against approval of a product with questionable cycle control.

In summary, I agree with the primary clinical reviewer for Lybrel™ and recommend that this product not be approved because of a demonstrated lack of efficacy and poor cycle control. Short of new clinical trial data in the US population which demonstrate an acceptable overall (user failure + method failure) Pearl Index and method failure Pearl Index, I do not believe that the Sponsor can satisfy the doubts regarding the efficacy of this product."

4.0 Division Director's Comments and Conclusions

After reviewing the memoranda of the primary and secondary reviewers, DRUP inquiries to Wyeth, and Wyeth's written and verbal responses to DRUP's communications and many of the past regulatory documents and decisions regarding contraceptive products, I have reached the opinions expressed in section 4 of this document in which I disagree with the reviewers on many points. However, because their analyses and opinions raise important issues related to women's health, specifically, contraceptive issues, I believe a public forum including outside contraceptive experts and other stakeholders should be convened to further discuss this application.

I believe that this forum is additionally important because there has been no public discourse sponsored by FDA, for some time, that has addressed these issues and guidance to sponsors regarding analyses and conduct of contraceptive trials may have been inconsistent or evolved due to changing science over the years.

4.1 Contraceptive efficacy: The reviewers maintain that the PI of 2.38 from study 313 is too high to allow approval of Lybrel because a PI above 2 or perhaps 1.5 indicates that a oral contraceptive is not efficacious. The medical team leader states in her review that this "product not be approved because of a demonstrated lack of efficacy."

There is no clear regulatory guidance to sponsor's regarding efficacy standards in the form of the upper limit of the point estimate (or 95% confidence intervals) of PI as calculated from the data derived from contraceptive trials. Furthermore, the point estimate of the PI in trial 313NA is lower than other approved products. In addition, since most contraceptive trials are single armed relying on historical controls, I do not believe one can determine whether a PI of 2.38 calculated from data in one trial truly represents inferior effectiveness compared to another trial in which a product's PI is determined to be 2 or even 1.5.

The reviewers reject the inclusion of trial 315EU in a combined analysis in order to calculate the PI for Lybrel. They also appear to dismiss this trial altogether in terms of supporting efficacy. The primary reviewer does not include any information from this

trial in the efficacy section of his Executive Summary of his review. The medical team leader states that "This trial was never intended to support effectiveness in the US. It is markedly underpowered in terms of a US study which requires 10,000 cycles and at least 200 subjects completing 13 cycles".

Trial 313NA includes about 12,500 cycles in the single continuous treatment arm. Trial 315EU includes about 2,500 cycles in each of the continuous and cyclic treatment arms. Both trials are one year in length (13, 28-day cycles). The point estimate and spread of the two sided 95% confidence intervals will reveal the precision of the trial results, regardless of the number of cycles.

While I believe that is debatable as to whether or not trial 315EU should be included in a meta-analysis with trial 313NA, I further believe that trial 315EU lends strong supportive evidence for the effectiveness of Lybrel. The conduct of trials 315 EU and 313NA are essentially the same, although there are population differences that have been mentioned previously. The PI for Lybrel in trial 315EU is **0.42 (95% CI: 0.01, 2.36)** and the PI for the cyclic comparator, Alesse (an approved US product) is **1.43 (0.29, 4.19).** I believe that the analytic results of trial 315EU indicate that the contraceptive efficacy of Lybrel is comparable to Alesse.

Other significant factors that can affect the efficacy outcome of a contraceptive trial and further confound cross trial comparisons are:

- Differing methods of determining the estimated date of conception (EDC). These methods have become more accurate recently.
- Populations that may differ by such factors as age, weight, compliance, and ethnicity. *Subjects in 315EU weigh less than those in 313NA.*
- Dose of the product. *Lybrel is a low dose product*
- Variable methods of calculating the PI

    Definition of factors that exclude some cycles for inclusion in PI calculation such sexual activity, condom use, pill compliance issues, etc.

    Factors that determine which pregnancies are, in fact, "on treatment." Should a pregnancy be included in the calculation of the PI only if it occurs during the period that the pills are actually being ingested or should the pregnancy be included in the calculation if the EDC occurs 14 or 7 days after pill ingestion is stopped per protocol (posttreatment)? I believe that the physiologic alterations affected by Lybrel as demonstrated in phase 2 trials would support counting pregnancies only until 7 days after cessation of treatment. One could further argue, however, that eliminating the pregnancies that occur 1-7 days posttreatment from the calculation of the Pearl index is also appropriate.

    Regarding study 313NA, there were 2 pregnancies 7 to 14 days posttreatment and 2 pregnancies between 1 -7 days posttreatment. I calculated the PI as 2.17 if one discounts the pregnancies which occurred 7-14 days post treatment. If one further discounts the pregnancies that occurred between 1 and 7 days posttreatment, the PI is 1.96

- Meta-analysis of multiple trials for calculation of the PI
- Length of trial

Other issues related to contraceptive efficacy that are highlighted by this application that deserve public discussion include

- Relative importance of user and method failures for a particular product
- The issue of alternate methods to calculate contraceptive efficacy such as life table analysis.
- The place of active controlled versus historically controlled trials in determine contraceptive efficacy.

4.2 Cycle control: The reviewers state that "the cycle control, in the form of sustained amenorrhea, for this continuous use oral contraceptive is poor." My opinion is that the determination of whether cycle control is adequate (or poor) should be made by the woman and her health care provider. As the trials submitted with this NDA progressed, an increasing proportion of women become amenorrheic or reported spotting not requiring any sanitary protection. It is difficult to compare bleeding between trials and certainly even more difficult to compare cyclic and continuous products. Standardizing methods for bleeding assessment could be explored in the public forum.

Of the women who began trial 313NA, 25% were amenorrheic at cycle 13 and 33% had only spotting at most. In trial 315 EU, 33% of those who started the trial were amenorrheic at week 13 and 45% had no more than spotting. Clearly there are a significant proportion of women who experienced reduced or eliminated cyclical or intermenstrual bleeding. Perhaps a Patient Reported Outcome instrument might be the best metric to determine the clinical significance of the improvement in health-related quality of life that this and other extended cycle products achieve.

4.3 Discontinuations

The primary and secondary medical reviewers state that "The discontinuation rate of 56.8% is the highest rate the Division has reviewed in regards to a combination oral contraceptive". The review team are referring to study 313NA. The discontinuation rate in 315EU was 33% (22% in the cyclic arm). It may well be that discontinuation rates for extended cycle regimens are higher than cyclic regimen. In the case of extended cycle products, I suspect that if women are expecting little or no vaginal bleeding, they may become discouraged and drop out of the trial because the desired effect is not achieved. It's relevant to note that trials for both oral and parenteral Progestin only contraceptives, which are know to cause significant "unanticipated bleeding", may also have high discontinuation rates. The discontinuation rates, for the two approved extended cycle regimens, which are taken continuously for 84-days (approximately 3-cycles) as opposed to an indefinite continuous use product such as Lybrel, are 40% for Seasonale and 50% for Seasonique.

Finally, one must remember that caution should be exercised in making cross-trial comparisons regarding discontinuation rates for some of the same reasons that were mentioned regarding cross trial comparisons of Pearl indices. (See section 4.1)

4.4 General Conclusion of Division Director: The medical team leader states as follows "I agree with the primary clinical reviewer for Lybrel and recommend that this product not be approved because of demonstrated lack of efficacy and poor cycle control…In this reviewer's opinion, the enormous public health impact of unintended pregnancies linked to discontinuations of oral contraceptives because of poor cycle control argues heavily against approval…"

I believe that it is not at all clear that this product has a "demonstrated lack of efficacy" for the reasons that I discussed in section 4.1.

This product provides a specific alteration in cyclical bleeding that many women perceive as positive. It should be determined by the women and her health care provider, after reviewing the facts related to the discontinuations, bleeding patters and Pearl index whether or not the risks and benefits are appropriate.

5.0 Regulatory action

This application is approvable. Before the application may be approved, however, it will be necessary for the sponsor to address the following:

1. The application does not contain sufficient stability data to support approval of the product manufactured using the revised [redacted] method. Submit 3 months of real time and accelerated stability data on the three lots of drug product manufactured by the revised [redacted] method. b(4)

2. Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application.

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/s/

Daniel A. Shames
6/27/2006 12:55:58 PM
MEDICAL OFFICER

5/22/07

DIVISION DIRECTOR (acting) MEMORANDUM
DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

Subject: NDA 21-864 – Lybrel™ (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg tablets) for Prevention of Pregnancy in Women

Background

Lybrel (levonorgestrel [LNG] 90 mcg/ethinyl estradiol [EE] 20 mcg) tablets is a combination oral contraceptive drug product that is to be taken once daily without interruption. This dosing regimen differs from that for previously approved combination oral contraceptives which are taken in a cyclic manner. The usually dosing regimen for cyclic combination oral contraceptives consists of 21 or 24 days of active tablets followed by 7 or 4 days of placebo tablets, respectively. This regimen generally results in cyclic scheduled menstrual bleeding every 28 days. Because some women prefer not to have cyclic monthly bleeding, "extended" dosing regimens, which result in fewer scheduled periods of bleeding, have been developed. Two products that consist of 84 days of dosing with LNG 150 mcg/EE 30 mcg tablets followed by either 7 days of placebo tablets (Seasonale) or 7 days of 10 mcg EE tablets (Seasonique) are approved for marketing in the U.S. Women who use these products for prevention of pregnancy can expect to have 4 scheduled periods of bleeding per year. However, many women using these products experience unpredictable breakthrough bleeding or spotting, particularly during the first several months of use. These women need to consider the benefit of fewer regular scheduled periods of bleeding (4 per year) against the inconvenience of unscheduled or unplanned breakthrough bleeding and spotting.

Lybrel was developed with the expectation that it (1) would be a safe and effective combination oral contraceptive and (2) would produce amenorrhea or minimal unscheduled breakthrough bleeding or spotting.

Regulatory History

The original NDA for Lybrel was submitted on May 27, 2005. Based on their respective reviews of the original NDA submission, both the primary Medical Reviewer and the Clinical Team Leader recommended that Lybrel not be approved. Both of these medical officers had similar concerns that related to efficacy, bleeding patterns, and the discontinuation rate in the primary clinical trial (Study 313-NA). The Division Director, in his review, raised a number of issues that questioned the conclusions of the primary review team. On June 26, 2006, an Approvable Action for NDA 21-864 was taken. The Approvable Letter identified the following clinical deficiencies:

> *"Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application."*

A Complete Response to the Approvable Letter was submitted to the Division of Reproductive and Urologic Products (DRUP) on August 22, 2006.

As the acting Director of DRUP, I have the delegated authority to Approve/not Approve Lybrel for marketing. I have requested, however, that this decision for Approval/non-Approval of Lybrel remain with Dr. Shames, the former Director of DRUP and the present Deputy Director of the Office of Drug Evaluation III (ODE III). I have made this request because of Dr. Shames' long and ongoing involvement with this NDA and his interactions with the primary review team from the time that the original NDA was submitted in May 2005. Although I will not make the decision to Approve/not Approve Lybrel for marketing, I have conducted an independent review and assessment of the efficacy data submitted by the Applicant in support of the NDA. I also have reviewed the safety profile for Lybrel (based largely on the reviews of the primary Medical Reviewer [Dr. Price] and the Clinical Team Leader [Dr. Slaughter]). Lastly, I have reviewed the final labeling submitted by the Applicant on May 21, 2007.

Overview of Phase 3 Clinical Trials

Data were submitted from two multicenter, one-year Phase 3 clinical trials that enrolled generally healthy women, 18-49 years of age, who were at risk of becoming pregnant.

Study 313-NA. Study 313-NA, the primary efficacy and safety study, was an open-label, single-arm trial conducted at 80 sites in North America (U.S. and Canada). Of the 2,134 subjects who took at least one dose of study drug, 77% were Caucasian, 10% were Black, and 9% were Hispanic. The mean weight of the subjects was 70.38 kg.

Study 315-EU. Study 315-EU, a supportive study, was a two-arm, open-label comparative trial of Lybrel vs. a cyclic regimen of LNG 100 mcg/EE 20 mcg tablets for 21 days followed by placebo tablets on days 22 to 28. The comparator is marketed as Loette in the European Union (EU) and as Alesse in the U.S. Six hundred fifty-one (651) subjects were randomized and 641 subjects took at least one dose of study drug: 323 in the Lybrel arm and 318 in the LNG 100 mcg/EE 20 mcg cyclic regimen arm. Of the 641 subjects who started study drug, 96% were Caucasian. The mean weight of subjects was 63.86 kg.

Efficacy (Prevention of Pregnancy)

Efficacy (more precisely the estimate of the risk of getting pregnant) was expressed in terms of the Pearl Index and a life table analysis of the probability of pregnancy within one year. The Pearl Index is based on the number of pregnancies per 100 women-years of use. Efficacy was assessed by the number of pregnancies that occurred after the onset of treatment and within 14 days of the last dose of study drug.

Study 313-NA. Among subjects ≤ 35 years of age, there were 23 pregnancies (4 of these occurred during the interval 1 to 14 days after the last day of pill use) during 12,572 cycles (28-day pill packs) of use. The resulting Pearl Index was 2.38 (95% CI: 1.51, 3.57) and the one-year life table pregnancy rate was 2.39 (95% CI 1.57, 3.62). Pill pack cycles during which subjects used back-up contraception or were not sexually active were not included in these calculations. Among women ≤ 35 years of age who took the pills completely as directed, there were 15 pregnancies (method failures) resulting in a Pearl Index of 1.55 (95% CI: 0.87, 2.56); the one-year life table pregnancy rate for these subjects was 1.59 (95% CI 0.95-2.67).

Study 315-EU. The efficacy analysis among women ≤ 35 years of age included 2,756 Lybrel 28-day pill packs and 2,886 cyclic comparator 28-day pill packs. There was one pregnancy in the Lybrel group that occurred within 14 days following the last dose of study drug. There were 3 pregnancies in the cyclic comparator group. The Pearl Index was 0.51 (95% CI: 0.01, 2.82) for the Lybrel group and 1.43 (0.29, 4.17) for the comparator group. The respective one-year life table pregnancy rates were 0.62 (95% CI: 0.09, 4.35) for the Lybrel group and 1.47 (0.48, 4.49) for the comparator group.

Conclusions. The Applicant has provided substantial evidence that Lybrel is effective for the prevention of pregnancy when used in accordance with proposed labeling. There is, however, disagreement within the Division, based on the Pearl Index of 2.38 in Study 313-NA, as to whether Lybrel has comparable efficacy as other low dose combination oral contraceptives previously approved by the Division. Without an adequately powered non-inferiority comparative trial, this disagreement cannot be answered with certainty. However, there is no suggestion from Study 315-EU that Lybrel was less effective than the active comparator (LNG 100 mcg/EE 20 mcg tablets). The active comparator, marketed as Alesse in the U.S., is widely accepted as a safe and effective combination oral contraceptive.

The Pearl Index of 2.38 also is numerically comparable to that for Estrostep (Pearl Index of 2.4) and numerically lower than that for Ortho tri-Cyclen Lo (Pearl Index of 2.67) in the clinical trials that resulted in U.S. approval of these latter 2 products. Lastly, at the meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) in January 2007, the members of the committee were asked if there was a specific Pearl Index above which a combination oral contraceptive should not be approved. There was extensive discussion of this issue but most members declined to provide a specific value. The committee chairman, summarizing the view of the members stated that "... *the committee was unanimous in its desire to make clear that arbitrary limits be avoided in order to promote the widest range of new contraceptive products being developed and brought to the market.*" ... "*Most abstained from giving an exact point estimate or upper confidence interval. The key point to emphasize is that you have to provide all the information to the clinician and the patient in an easily understandable format in labeling and then let them make the final decision on which product is most appropriate for the patient (i.e., caveat emptor).*"

Inhibition of Menses (Bleeding Profile)

In the clinical development program for Lybrel, the Applicant used the following definitions for vaginal bleeding:

- Bleeding: sanitary protection was required;
- Spotting: some bleeding but no sanitary protection was required; and
- Amenorrhea: no bleeding or spotting during the 28-day interval of interest.

Study 313-NA. The number (%) of subjects for whom bleeding data were available and who had amenorrhea or no bleeding (amenorrhea or spotting only) during each of the 28-day pill pack intervals in Study 313-NA increased with duration of use as shown in the following Table.

Number (%) of Subjects with Amenorrhea or No Bleeding (Amenorrhea or Spotting Only)

		Amenorrhea		No Bleeding (Amenorrhea or Spotting Only)	
Pill Pack	N	n	%	n	%
1	2048	48	(2.3)	124	(6.1)
2	1947	450	(23.1)	936	(48.1)
3	1671	446	(26.7)	878	(52.5)
4	1545	502	(32.5)	927	(60.0)
5	1469	540	(36.8)	943	(64.2)
6	1403	555	(39.6)	929	(66.2)
7	1220	546	(44.8)	864	(70.8)
8	1173	600	(51.2)	891	(76.0)
9	1144	601	(52.5)	870	(76.0)
10	1070	584	(54.6)	841	(78.6)
11	1014	597	(58.9)	821	(81.0)
12	977	604	(61.8)	816	(83.5)
13	860	505	(58.7)	679	(79.0)

The percentage of subjects with amenorrhea was 23.1% during use of 28-day Pill Pack 2, 44.8% during use of Pill Pack 7 (mid-point of the study), and 58.7% during use of Pill Pack 13 (i.e., the final 28 days of the one year study). At Pill Pack 13, however, less than half of the subjects who started treatment were still in the study. The increase in the percentage of subjects who achieved amenorrhea with increasing duration of use is likely due to both improved bleeding profiles, per se, and premature discontinuation of subjects who did not have an acceptable bleeding profile.

Unscheduled bleeding in women using Lybrel in the Phase 3 clinical trials was not associated with clinically meaningful changes in hemoglobin or hematocrit values.

Conclusions. Based on the data provided by the Applicant, it cannot be predicted in advance if a woman is likely to develop amenorrhea or have an acceptable bleeding pattern while using Lybrel. Women choosing to use Lybrel will likely need to tolerate unscheduled bleeding and spotting, especially during the first several months of use. Each user of Lybrel will need to decide for herself if a bleeding profile other than amenorrhea will be acceptable to her. It will be important that women be adequately educated by their healthcare provider and through clear product labeling regarding unscheduled bleeding prior to electing to use the product.

At the January 2007 meeting of the ACRHD, members were asked the following: *"In reviewing extended regimens, how should the Division balance a decrease in scheduled bleeding against an increase in unscheduled bleeding?"* The Chairman's response was *"The committee felt the FDA does not need to balance these issues; rather they need to provide the relevant information to patients and clinicians in labeling."* In a related question, the Committee was asked: *"How should the Division assess the impact of unscheduled bleeding on product acceptability?"* The response was *"... the FDA should approve products based on their demonstrated safety and efficacy and allow the patient and clinician to determine acceptability..."*

Premature Discontinuations

Study 313-NA. Of the subjects who started Lybrel, 1,213 (56.8%) discontinued prematurely before one year, including 102 (4.8%) discontinued by the Applicant for early study closure.

The most common reasons for premature discontinuation were adverse event (17.0%), subject request (15.7 %), and lost to follow-up (10.4%). Bleeding-related reasons accounted for 18.0% of the premature discontinuations. These bleeding-related events accounted for approximately 50% and 60% of the discontinuations in the categories of *adverse event* and *subject request*, respectively.

Study 315-EU. Overall, 176 (27%) of subjects discontinued prematurely from the study: 107 (33%) subjects in the continuous use (Lybrel) treatment group and 69 (22%) subjects in the 21-day cyclic regimen. Bleeding-related reasons accounted for 15.8% (Lybrel group) and 4.7% (cyclic group) of the premature discontinuations. Bleeding-related discontinuations accounted for the overall difference in premature discontinuations between the 2 treatment groups.

Conclusions. The discontinuation rate of 56.8% in Study 313-NA is higher than that observed in other Phase 3 trials reviewed by DRUP that have supported marketing approval of a combination oral contraceptive. Eighteen percent (18%) of these discontinuations were related to bleeding. The percentages of subjects who discontinued prematurely in the clinical trials for Seasonale and Seasonique (the only presently approved combination oral contraceptives with continuous active dosing cycles longer than 26 days) were 40% (Seasonale) and 50% (Seasonique). It is likely that most women entered into the clinical trials for Lybrel, Seasonale, and Seasonique with the expectation that they would have no (Lybrel) or fewer (Seasonale and Seasonique) planned menstrual periods and little unscheduled bleeding. If their expectations were not met, they likely discontinued prematurely from the clinical trial.

It cannot be predicted in advance if a woman is likely to develop amenorrhea or have an acceptable bleeding pattern while using Lybrel. Therefore, it will be important that women be well informed by their healthcare provider and through clear product labeling and market advertising regarding unscheduled bleeding prior to electing to use Lybrel. If women are well informed that they will likely need to tolerate unscheduled bleeding and spotting, especially during the first several months of use, many may choose not to use the product. Those who do choose to use Lybrel should have more realistic expectations and may be less likely to discontinue using Lybrel because of bleeding-related issues. Both healthcare provider and patient labeling for Lybrel clearly describe the bleeding profiles likely to be experienced by women who choose to use Lybrel.

Safety Profile

Both the primary Medical Reviewer and the Clinical Team Leader found the safety profile for Lybrel to be acceptable. I concur with their assessment.

Labeling

The DRUP as well as ODE III worked with the Applicant to ensure that labeling would provide clear information regarding the efficacy, bleeding patterns, and discontinuation rates in the clinical trials with Lybrel. Approved labeling should enable women and healthcare providers to make informed decisions regarding the use of Lybrel.

Recommendation regarding Approvability

The Applicant has provided substantial evidence that Lybrel is effective for the prevention of pregnancy when used in accordance with proposed labeling. The safety profile of Lybrel is acceptable for a combination oral contraceptive. Labeling submitted by the Applicant on

May 21, 2007 is acceptable. I therefore recommend approval of Lybrel for the indication of *"prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception."* I believe that this recommendation is consistent with the general guidance provided by the Advisory Committee for Reproductive Health Drugs in January 2007. Lybrel will likely provide a desired alteration in menstrual bleeding patterns in approximately 50% of women who continue to use the product for one year. It should be determined by the woman and her healthcare provider, after reviewing the facts related to efficacy, bleeding patterns, and discontinuation rates, as to whether or not the risks and benefits of Lybrel are appropriate.

Phase 4 Studies. The DRUP has recently initiated a policy of requesting that Applicants for new hormonal contraceptive products conduct a post-approval study to assess thrombotic risk if the new product contains either a new molecular entity or has a dosing regimen that differs significantly from previously approved products. Lybrel is taken daily, without any break in dosing, and therefore represents a significant new dosing regimen for a combination oral contraceptive. Wyeth has agreed to conduct a post-approval claims database safety study to compare the risk for thromboembolic events in users of Lybrel to the risk in users of cyclic combination oral contraceptives.

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/s/

Scott Monroe
5/22/2007 03:52:04 PM
MEDICAL OFFICER