

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-864**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

### Team Leader Memorandum Complete Response - Lybrel™

<b>NDA:</b>	<b>21-864</b>
<b>Drug:</b>	<b>Lybrel™</b>
<b>Dosage Form/Route:</b>	<b>Tablet/Oral</b>
<b>Strength:</b>	<b>90 µg levonorgestrel/ 20 µg ethinyl estradiol – daily continuous administration</b>
<b>Applicant:</b>	<b>Wyeth Pharmaceuticals, Inc.</b>
<b>Original Submission Date:</b>	<b>May 27, 2005</b>
<b>Original Medical Officer Completion Date:</b>	<b>March 22 2006</b>
<b>Original TL Memorandum:</b>	<b>May 22, 2006</b>
<b>Complete Response (CR) Receipt Date:</b>	<b>August 22, 2006</b>
<b>Medical Officer Review Completion Date:</b>	<b>April 26, 2007</b>
<b>Date of CR Team Leader Memorandum:</b>	<b>May 14, 2007</b>

Materials reviewed for this Memorandum were: Complete Response to Approvable for NDA 21-864, Major Amendment, dated December 22, 2006, Original Cycle Reviews of the Medical Officer, Statistician, Group Leader and Division Director, Transcripts and Official Meeting Minutes of the Reproductive Health Advisory Committee, January 23-24, 2007.

Executive Summary:

This reviewer recommends that Lybrel™ not be approved based on what I believe is an efficacy profile that can be characterized as marginal at best and poor at worst (Pearl Index of 2.38) relative to a standard for acceptable failure rates, expressed as a Pearl Index of 1 - 2, for “all users” in a clinical trial setting.. Further, a secondary analysis of “perfect use” (or method) failure rates yields a Pearl Index of 1.55; substantially greater (5 times) than that of the 0.3% as stated in the literature (*Hatcher et al. Contraceptive Technology-18<sup>th</sup> revised edition*) for method failures. In addition, contrary to the intended non-contraceptive benefit of sustained amenorrhea, the primary clinical trial for this product demonstrated that 41.3% of subjects were not amenorrheic at the end of the 13<sup>th</sup> pill pack (or approximately 1 year) of use. Two cases of the serious adverse event of pulmonary embolus (one in the primary clinical trial, Study 0858A2-313-NA, and one in a second study conducted under the IND) were seen in 2,851 subjects submitted in the safety-update for Lybrel™. The risk of a pulmonary embolism is a known adverse event under the spectrum of venous thromboembolism which can occur with estrogen therapy. The incidence rate of 2/2,851 (0.70/1000subjects) is not an alarmingly higher rate than that seen in previously-approved combined oral contraceptives products. This reviewer finds the safety profile to be acceptable.

Regulatory History (Cycle 1 Determination and Conclusions)

NDA 21-864 for Lybrel™ was submitted on May 27, 2005. At the conclusion of the first cycle of review, there were outstanding Chemistry Manufacture and Controls (CMC) issues as well as internal disagreement between the Clinical Reviewing Team (see Primary Medical Officer Review, dated March 22, 2006 and Group Leader Memorandum, dated May 22, 2006) and the then Division Director of DRUP (see Division Director Memorandum, dated June 26, 2006) on whether this product demonstrated an acceptable efficacy profile and the impact of the rate of study discontinuations and unexpected bleeding upon approvability of the product. Safety was not considered an issue by either the Clinical Reviewing Team or the Division Director.

Based on the information provided in the NDA from the primary, mostly U.S.-conducted, clinical study, Study 0858A2-313-NA, and previously established standards in the Division for assessing an acceptable level of efficacy (Pearl Index less than or equal to 2.0), the Clinical Reviewing Team concluded that the Pearl Index and Life Table Method of 2.38 (95% CI 1.51, 3.57) and 0.0348 for the population of “all users” (typical + perfect users) 35 years of age and younger representing 12,572 cycles and 9,180, respectively, did not provide an acceptable level of efficacy for approval. Further, supporting the Clinical Review Team’s assessment of a non-acceptable level of efficacy was the “perfect use” (Method) failure rate with Pearl Index and Life Table rates of 1.55 (95% Confidence Interval 0.87, 2.56) and 0.0278 in the population of women age 35 years of age and younger who had used the product faithfully as instructed. Per the published literature and textbooks on contraception, the “perfect use” of combined oral contraceptives should be less than 1%. These “perfect use” failure rates for this hormonal contraceptive were noted to be not much better than the “perfect use” rates a woman could be expected to achieve with non-hormonal non-drug methods such as condoms (2%).

The Clinical Reviewing Team further determined that the Pearl Index and Life Table failure rates of 0.51 (95% CI 0.01, 2.82) and 0.0110 in 2,564 and 1,977 cycles, respectively, from a second study conducted in Europe, Study 0858A2-315-EU, did not over ride the findings in the primary Phase 3 U.S. trial and, did not constitute sufficient evidence to warrant a recommendation to approve. The Clinical Reviewing Team held that Study 0858A2-315-EU was not intended to support effectiveness in the U.S. and that the study was underpowered in terms of a U.S. study to support contraception which requires 10,000 cycles and at least 200 subjects completing 13 cycles.

In Study 0858A2-313-NA, the primary efficacy and safety study, the incidence of amenorrhea at pill pack 13 was 58.7%. At pill pack 13, 41.3% of subjects exhibited bleeding and/or spotting (2.7% exhibited bleeding with no spotting and 20.2% had spotting with no bleeding; and it is assumed that the remaining 18.4% had both bleeding and spotting). In this same study, 56.8% of subjects discontinued the study. Of the 17% of subjects who discontinued because of an adverse event, 49.8% of these were for bleeding. Based on this evaluation, the Clinical Reviewing Team determined that Lybrel™ had an unacceptable cycle control (bleeding) profile and the discontinuation rate of the primary study was believed to be too high, not representative of usual contraceptive trials and reflective of poor cycle control.

The Division Director expressed the following:

- “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”.
- “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”.
- “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.”.....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.”
- “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 patterns and Pearl index whether or not the risks and benefits are appropriate.”

On June 27, 2006, an Approvable letter was issued to the Sponsor. This decisional letter stated that before the application may be approved, it will be necessary for the Sponsor to address:

1. The application does not contain sufficient stability data to support approval of the product manufactured using the revised \_\_\_\_\_ method. Submit 3 months of real time and accelerated stability data on the three lots of drug product manufactured by the revised \_\_\_\_\_ method.
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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Further, the Approvable letter stated that when the Sponsor responds to the previously noted concerns, they should include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

A complete response was received by Wyeth Pharmaceuticals on August 22, 2006. On December 22, 2006, the Agency received a major amendment which proposed to change the current \_\_\_\_\_ manufacturing process \_\_\_\_\_

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Information Considered for Complete Response:

Safety Update:

The safety update includes data from all on-going clinical studies of Lybrel™, regardless of the indication, dosage form or dose level. The studies reported on were:

- Study 0858A2-313-NA - post-study pregnancy and return to spontaneous menses results
- Study 0858A2-314-NA - study of time to return to spontaneous menses or pregnancy in subjects with 6 to 13 pill packs of exposure to Lybrel in Study 0858A2-313-NA
- Study 0858A2-320-CA - 1 year extension study of Study 0858A2-313-NA
- Study 0858A2-316-NA - study conducted under IND 63,910 evaluate Lybrel™ for
- Study 0858A2-322-US - study conducted under IND 63,910 evaluate prevention of severe cycle related symptoms
- Study 0858A2-318-WW - Phase 3 study worldwide (80 sites) to assess Lybrel™ (vs. placebo) on a 21-item daily score

Please see the Medical Officer Review for a detailed presentation of the Safety Update information.

A total of 2851 subjects on Lybrel™ were reported on. No deaths were reported.

Serious adverse events include:

- 2 cases of cholelithiasis - one case (Study 230-CA) not judged to be serious but assessed as possibly related to study medication; resolved with surgery performed on day 694 of treatment; second case occurred during single blind washout interval for Study 322-US
- 1 case of anxiety and asthenia (Study 230-CA) - judged unrelated to study medication
- 1 attempted suicide (Study 230-CA) - judged unrelated to study medication
  
- 1 ruptured ovarian cyst (Study 322 US) – unrelated to study medication
- 1 acute appendicitis (Study 322 US) – unrelated to study medication
- 1 automobile accident (Study 322 US) – unrelated to study medication

- 1 pulmonary embolus ((Study 322 US) in 123.8 kg, 42 year old at 86 days post treatment

#### Advisory Committee

A meeting of the Advisory Committee (AC) for Reproductive Health Drugs to discuss General Topics for Hormone Contraceptives (referred to subsequently in this review as Hormone Contraceptive General AC) was held on January 23 and 24, 2007. As can be inferred from the previous sentence, this meeting was designed and conducted to address general topics that the Division confronts in its review of all hormone contraceptive products. Although the drug product Lybrel™ was not specifically discussed in this meeting, some of the issues discussed were relevant to issues with this review. The Division presented the AC with a series of topics and questions for discussion. With two exceptions (one formal vote and one mock vote), the AC was *not asked to* and *did not vote* on these questions. Therefore, it is not possible to say that the majority of the responses were agreed or disagreed by vote. The Chair of the AC, Dr. Charles Lockwood, did attempt to summarize the discussion of each question or sets of questions after the discussion took place. Readers of this review are urged to review the Transcripts and the Final Summary Minutes (as approved by Dr. Lockwood) of this two-day meeting which are available to the public at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>.

The following is a presentation of the Chair's summation of the discussion points as recorded in the transcripts and Summary Minutes and some of the discussions by AC members that I considered important to include. This presentation is not intended to distill or be a complete presentation of each member's discussion recorded in those transcripts.

- Should entry criteria be more reflective of actual clinical prescribing regarding BMI, smoking, and family history of thrombosis or thromboembolism?

There seems to be consensus that it is virtually impossible to obtain adequate and accurate safety information given the enormous size of a trial that will be required.—  
**Dr. Lockwood for the AC**

There seems to be consensus, as well, that more real-world testing is necessary and that the inclusion criteria for clinical trials ought to be expanded to include women that smoke, women that have a much wider range of BMIs.—**Dr. Lockwood for the AC**

- The Division has seen different efficacy results in foreign studies compared to U.S. studies (often better efficacy results in Europe). Should a certain minimum percentage of the subjects in Phase 3 studies be studied at U.S. sites?

Studies from Europe and other areas of the world are potentially very valid and useful, and a careful analysis of those studies may indicate areas where their applicability to the real world, to typical use in the United States may not have been adequately assessed.—**Dr. Lockwood for the AC**

For drug that will be marketed in the US, the clinical trial should enroll a minimum percentage or a minimum number of US subjects.—summation from **Final Summary Minutes**

- Are there cultural or physical attributes in foreign populations that would render contraceptive study data from such population less applicable to the US population?

The general opinion was yes.-summation from **Final Summary Minutes**

- Should a certain percentage of the study population represent “fresh starts” as opposed to switchers?

The general opinion of the committee was no. However, Switchers may have lower pregnancy rates than fresh starts. Active controls may mitigate this concern.- summation from the minutes.-summation from the minutes. -summation from **Final Summary Minutes**

- Is there a role for active controlled trials; if so, under what circumstances?

I think that it is silly in this day and age to do a trial, a study that we call a trial, and make claims about anything based on historical controls.....we should stop talking about approval of products based on historical controls. —**Dr. Petitti**

I think it is fair to say that is the consensus of the group.—**Dr. Lockwood for the AC**

I agree very strongly with the comments about active comparator, but would note that one does have to label the product with a pregnancy rate, so the active comparison does alone does not give you all of the information that you have to have.—**Dr. Stadel**

There is a difficult issue of establishing a band of acceptability for active comparators or the possibility even of saying that there are categories of OCs one that has been tested against products with the following established level and the other which has been tested against the lower level.—**Dr. Stadel**

I think it is very important these trials be done double-blind wherever possible, using the double-dummy technique, which means you have got to pick a single control entity.—**Dr Tobert**

After much discussion, the Chair decided to call for a formal vote on this question? Results: Yes=19; No=0; Abstain=0.-see transcript and summation from **Final Summary Minutes**

- Should electronic diaries be recommended for pivotal contraceptive clinical trials?

The consensus there (for electronic diaries) is recommended, but not required.—**Dr. Lockwood for the AC**

- Would information obtained from validated patient reported outcome instruments be more useful in contraceptive trials?

The consensus is that if such instruments were available, they would be extremely useful, and that the ball is back in the FDA's court to perhaps help develop that instrument or lobby for research in that area, and so forth, but that it seems going beyond just a termination rate, to determine satisfaction would be very useful.—**Dr. Lockwood for the AC**

- Could a validated PRO instrument, Patient Reported Outcome instrument, be used to obtain secondary labeling claims for superiority, for example, better cycle control?

Concerns were expressed regarding issues of internal versus external validity for making such claims. The committee also expressed concerns that until standardized definition of bleeding patterns are established; developing a validated PRO will be difficult, which limits the committee's ability to answer the question-summation from **Final Summary Minutes**

- Pearl Index versus life table analyses: What are the relative merits of each approach? Are there situations where one approach should be favored over the other? If so, what are they? How should divergent pregnancy rates calculated by the Pearl Index versus life table methods be considered in the approval process and in labeling?

The general feeling of the committee is that the Pearl index, although providing simplicity is a less desirable analysis method in almost all circumstances. Life-table analysis should be the standard. -summation from **Final Summary Minutes**

- How should divergent pregnancy rates, obtained in U.S. and non-U.S. populations, be considered in the approval process and in labeling?

The committee expressed the view that if data from the U.S. and non-U.S. populations differ dramatically, the U.S. data should take precedence. -summation from **Final Summary Minutes**

- Should "on-study pregnancies" be defined to include only those pregnancies that occur while subjects are within the treatment cycle or also include those pregnancies with an estimated date of conception that may have occurred within a certain number of days after the end of the last treatment cycle (e.g., 2, 5, 14 days-where the treatment cycle is defined to include the pill-free interval following active treatment)?

On-study pregnancies should be limited to those in which conception occurred during the established treatment cycle.-summation from **Final Summary Minutes**

If yes, where should the cut-off be established or should it vary according to how reliably a drug inhibits ovulation

Covered in previous answer

- How can the life table analysis of pregnancy rates be adjusted for the use of back-up contraception midway through the exposure period, for example, back-up contraception used only during treatment cycle 6 in a 13-month treatment cycle?

The committee indicated there were 4 ways to handle the situation:

1. exclude (censor) the patient's data entirely
2. include the relevant data up to the point of censoring
3. include all cycles in which back-up contraception was not used
4. include all cycles as it more accurately reflects "real-world" usage

The data should be analyzed multiple ways, but the preference is to model the real world and include all the data, and assume it reflects typical use. Moreover, since strong preference would be given to active control trials in support of new applications such confounding was likely to occur in both the treatment and control arms to an equivalent degree.-summation from **Final Summary Minutes**

- How should the analysis of pregnancy rates be adjusted for the use of back-up contraception in extended cycle contraceptive trials? For example, in an 84/7 dosing

regimen, should an entire 91 day cycle be considered non-evaluable, or should only a 28 day portion of the cycle be excluded from consideration of at risk cycles?

The committee suggested analyzing the data with the back-up method data included, as well as with it removed, to discern any impact. Opinions included:

1. censor the subject's data at end of the last cycle before she began to use back-up methods
2. count it because all trials should be predicated on a pure intent to treat model
3. do not include data from the entire cycle (91 days)

Previous discussion excerpted from the summation from **Final Summary Minutes**. The options were based on a discussion of a controlled clinical trial.

In order to calculate perfect use data, you have to analyze the data in such a way as to exclude this confounding from multiple contraceptive use. —**Dr. Lockwood**

If we are in a comparative-trial situation that (ignoring condom use) is not going to be an issue because you should be non-differential on each arm. But, if you are going to the historical control, again, you have to decide what you are going to do with these people because you are measuring two different quantities, whether you leave them in or whether you take them out. —**Dr. Gillen**

I would strongly support that the primary endpoint be all cycles and all pregnancies, and the rest of these were secondary...the primary outcome measure, at least in all the trials I have seen, has been the intent-to-treat populations, so I have no reason to change that. —**Dr Trussel**

So, to summarize, we are being asked—really, the statisticians are being asked—to advise the rest of the panel. The actual study design characteristics that are required, intent-to-treat, seems to be universally agreed upon. I think everybody on the panel would agree that this is the ideal way to approach it. Life table analysis, no further discussion needs to be done on that, but the specifics of the life-table analysis, the specific type of life-table analysis and Kaplan-Meier, and then how to handle subgroup analysis. I guess, beyond just the issue of back-up contraception, theoretically, you could also parcel out high BMI's and other aspects to that. —**Dr. Lockwood for the AC.**

Mr. Chairman, I think you said that these active comparison trials would be analyzed on the intention-to-treat basis, but I don't think there actually can be a pure intention-to-treat. ....to try to answer the question from the FDA about what hypothesis should be for these comparative trials and I think it should be non-inferiority in most cases. —**Dr. Talbot**

I think if we are moving toward consensus, it is that the concept of perfect use is an anachronism, that there is no sort of perfect person, that there is substantial variability and fecundity related to age,....et cetera, et cetera, and that, even with perfect uses, there is likely to be significant variability in different population, that there might still be a valid effort to make in terms of secondary analysis. Primary analysis ought to be on actual use... There is universal acceptance of this modified intent-to-treat...there are lots of messy conditions in (the) real world with monogamous relationships, and serial monogamy and age factors that relate to monogamy versus use of barriers. But, again, a lot of these wash out with use of active controls, intent-to-treat, and life-table analysis and the ability to then do subanalysis.

- For historically controlled trials, should evaluation of pregnancy rate be based only upon the point estimate, the upper bound of the 95% confidence interval around that point estimate, or both?

No consensus was reached.-summation from **Final Summary Minutes**

- Is there a pregnancy rate that would be unacceptably high, regardless of the risk/benefit balance of the product?

If so, what would that rate be?

Discussions relative to this two-part question were held on both days of the meeting

Just to summarize what I think is the sense of the Committee, that they are uncomfortable giving you a specific number, that there really seems to be a mix of attitudes in terms of the requirement for documentation of much greater safety, or other benefits beyond safety, as being required to have been demonstrated from some of the Committee member to agree to a significant increase in the upper limit of efficacy.—**Dr. Lockwood for the AC-Day 1**

It seems to me there was somewhat of a consensus that as long as women are informed and providers are informed, that there isn't really a lower limit of *effectiveness* as long as it is communicated to the patients within the realm of other contraceptive choices—**Dr. Johnson-Day 1**

Very good point. I think caveat emptor was the message that everyone wanted to convey,—**Dr. Lockwood for the AC-Day 1**

On day 2 the Committee was pressed harder for it's responses to the question as to whether there is an unacceptably high rate and if so what is it.. A mock vote was taken:

We are going to put ourselves on the spot and we are going to answer question 15a, which is, is there a pregnancy rate that would be unacceptably high? We are going to define that both in terms of point estimates and intervals, and then we are going to modify whatever statement we want to make and we are going to go around the table to do that.....I hope everybody understood the way I worded this. I want the calculation of a point estimate, based on the Pearl Index, beyond what you will be uncomfortable approving the agent, and the upper limit that you would want an additional study to confirm in a more precise way in a Phase 4 setting what the actual number is likely to be. — **Dr. Lockwood for the AC-Day 2**

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|-------------------------|---|
| <b>Dr. Stadel –</b>     | I decline to answer with a number   |
| <b>Dr. Johnson -</b>    | 2,5, and 5  |
| <b>Dr. Petitti -</b>    | It is very clear from what we have heard that if the pill is no better, has no benefits over anything else, one could make an argument for accepting no difference, a delta of zero. Why do we need yet another contraceptive, if in fact, it doesn't have offsetting benefits. |
| <b>Dr. Gilliam –</b>    | I am fine with those numbers 2, 4, and 6 (point estimate of 2, delta of 4 and upper bounds of 6 to define limits for a P-4 study). The only thing that I want to add...are guidelines so that if a company could argue that the numbers become too outrageous...                |
| <b>Dr. Hilliard –</b>   | I am going to abstain   |
| <b>Dr. Perlmutter –</b> | I am not going to give you a number   |

- Ms. Shanklin-Selby** I am also abstaining
- Dr. Trussel –** I wouldn't go above a delta of 2 even though I am not a clinician... I would be willing to trade off efficacy for something else
- Dr. Gillen –** It is absolutely impossible for me to give you a margin for inferiority without knowing what the variability in the active control is. I can not do it..... So, first I would go back to historical met-analyses and first try to clear them up and clean them up as best I can, try and quantify the variability across the active control that I am going to choose, determine what the variability in that active control is, take the lower confidence limit of what that is, the worst-case scenario, and the I would start defining my delta of that because that is really going to put a bound on what I am willing to accept for a new treatment efficacy and what is coming up. On top of that, it is going to go with ..What are the safety profiles of this; what are the new potential benefits; if nothing else is going to benefit me why would I accept anything lower for an efficacy
- Dr. Blumenthal –** It depends on the characteristics of the agent and it depends on what the characteristics are relative to other agents
- Dr. Gibbs –** We have one convention that has stood the test of time and we use 95% to say that something is meaningful or significant. So I would say I would accept any value in effectiveness as long as the upper bound of that is 95% for a contraceptive to be considered highly effective (in a comparator trial)
- Dr. Westney –** Abstain
- Dr. Espey –** 95 % would be my cut-off. It is not just the clinician or us that feel that it is reasonable to have a tradeoff between efficacy and side effects but these advocacy groups feel the same way.
- Dr. Peterson –** I think that there are two issues that we have touched on that make it difficult for people to come up with a number. The problem is that we can each speak to our own perspective as providers but we really don't know what providers nationally might think because those data aren't available. Likewise we don't know what consumers nationally might see. If it is 2 % and we pick a delta of 4 and, let's say from my perspective, there would be a meaningful difference between 2 and 6, Then that is my perspective. I think while our perspectives will differ potentially, the guiding principle is that people deserve to be informed about that difference whatever the acceptability of that difference seems to be one that is not contested.
- Dr. Berenson –** ...If I have a patient that I am certain is going to take those pills every day and she can use any birth control pill on the market, I want to give her the one that works the best, that doesn't have more side effects than any other...if you want o know what doesn't matt, I would agree with about 5 % and there I am probably going to tell her they are pretty equally effective.

- Dr. Tulman –** I am going to decline to put any numbers around anything.
- Dr. Scott –** I wouldn't even put a limit on it.
- Dr. Bustillo –** If I were in the reproductive age range, tolerating something that would have a 5-time failure rate unless, as has been mention, you had a significant reason....I am worried about the slippery slope because what are we trying to do, we are trying to prevent pregnancy.....I don't know what the number is but I think that for me more than 5 times the pregnancy rate would be outrageous unless you had significant reason to want to prescribe that.
- Dr. Lockwood –** It depends. If this is an ordinary contraceptive....I think 2 is a very reasonable number. But if you tell me that it is going to do all the other things that it is likely to do it, there is biological plausibility for that argument or there is a frank indication for those other potential positive effects then I am not sure what the limit is. Caveat emptor would be in the labeling and people make their own decisions.

**Dr. Lockwood's summary:** I am going to take the Chair's prerogative and summarize our conversations regarding a number of discussions that were had. I think it is fair to sate that the consensus of this committee was to encourage the FDA, as they approach the assessment of sponsor applications, to have greater flexibility in terms of accepting an efficacy rate, such that we don't create artificial restraints to entry of new potentially efficacious and safer products and safer products and, at the same time, that there isn't creep of failure rates.

There was no consensus on a number. There was no consensus on the upper confidence interval. There was certainly no consensus on a point estimate. I think what there was consensus on was the concept that it depends. It depends on what the agent is being proposed, what the indications are, and what the potential biologically plausible benefits might be to that agent... I think that each drug has to be weighed in terms of its risks and benefits and there will be tradeoffs that will by necessity, have to be made in terms of safety and efficacy.

**Dr. Peterson:** I think that when we start getting into the realm of theory we can start arguing things a bunch of different ways.....So, if we start changing our thinking based on what might be, it creates a whole cascade of things that probably aren't good.

**Dr. Lockwood:** Dr. Gillen provided a very nice framework for how to approach that ( non-inferiority limit or margin) from a statistical standpoint by analyzing literature, conducting meta-analyses, determining the approximate confidence intervals and then establishing a priori what the sponsor intends to prove in terms of fitting within that interval.

- Should the Division approve lower-dose products that have apparent decreased efficacy and possible decreased risk of serious adverse events as compared to higher-dose products (e.g., 20 µg estrogen vs. 30-35 µg estrogen contraceptive products)?

The general opinion of the committee is yes. The bottom line is that the risks versus benefits need to be conveyed to the patient.-summation from **Final Summary Minutes**

- Can trial design be modified so as to provide results that are more reflective of actual effectiveness in the “real world”?

The committee would like trials to expand entry criteria to include adolescents, women with higher BMIs, under represented minorities, and other subpopulations. They would like clinical sites to be conveniently accessible in terms of location and the hours of operation to fit the needs of the study population.-summation from **Final Summary Minutes**

- Can trial design be modified so as to provide results that are more generalizable to U.S. subpopulations (e.g., enrolling more minorities and/or subjects from lower socioeconomic groups) who may have more real or perceived barriers that impact compliance?

The general opinion of the committee is yes, but there are cultural, language and logistical issues that need to be addressed so that minority subjects are approached in a more inclusive manner. The committee also suggested that there may be difficulty in enrolling enough subjects in those subpopulation groups to obtain meaningful information for them and therefore appropriate planning will be essential.-summation from **Final Summary Minutes**

- Should clinical trials investigate new technologies that may facilitate compliance in “real world” use?

The consensus of the committee is yes. In general, new technologies should be investigated and once validated should then be incorporated into clinical trials, but you should not use unproven technology and risk introducing another confounding variable.-summation from **Final Summary Minutes**

- Do the members of the Advisory Committee agree with the recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials proposed in the article by Mishell et al.?

The consensus is yes.-summation from **Final Summary Minutes**

- How should the Division assess the impact of unscheduled bleeding on product acceptability?

The committee felt that the FDA should approve products based on their demonstrated safety and efficacy and allow the patient and clinician to determine acceptability. However, some members posited that data on the relative occurrence of scheduled and unscheduled bleeding should be provided in the product labeling.-summation from **Final Summary Minutes**

- What objective measures beyond hemoglobin and hematocrit values, if any, should be employed to assess significant change in hematologic status.?

The committee recommends no other measures.-summation from **Final Summary Minutes**

- If the modified or extended dosing regimen does not expose a woman to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product what are the additional criteria that a Sponsor needs to meet to support approval for marketing?

It is difficult to predict in the pre-marketing setting what the long term safety implications of greater monthly quantities may be and therefore post-marketing surveillance is encouraged.-summation from **Final Summary Minutes**

- In reviewing extended regimens, how should the Division balance a decrease in scheduled bleeding against an increase in unscheduled bleeding?

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.-summation from **Final Summary Minutes**

- What cycle length should be used when analyzing cycle control in extended cycle products?

The established cycle length (e.g. 84/7) should be used when analyzing cycle control in extended cycle products. Some member suggested the FDA should convey in labeling that for the traditional 21/7 regimen that there are on average "x" number of days of scheduled bleeding and an average of "y" number of unscheduled bleeding days and similar language used for the extended regimens. Others suggested describing qualitatively what to expect about bleeding and how it may change over time.-summation from **Final Summary Minutes**

- What designs should be considered for Phase 4 studies of hormonal contraceptives and what are the strengths and limitations of each design (e.g., a more rigorous design but a delay in obtaining outcome data)?

These studies are expensive. If a company is trying to make a new indication or safety claims (e.g. that their product is indicated in women at higher risk for venous thromboembolism because it poses a lesser risk), they should perform a randomized clinical trial, a very carefully designed and conducted prospective cohort study, or a case-control study nested in a large cohort. For effectiveness, a prospective observational study of representative populations is permissible. For general safety issues, observational data is permissible. Refer to Dr. Petitti's presentation for more detail.-summation from **Final Summary Minutes**

- Phase 4 commitments have generally been confined to obtaining information primarily or entirely related to safety issues. Can such studies be designed to obtain a better estimate of true "actual use" product effectiveness?

The committee consensus is yes.-summation from **Final Summary Minutes**

- If so, how best can this information be obtained?

The general nature of the committee consensus was in support of the study designs discussed in Dr. Petitti's presentation.-summation from **Final Summary Minutes**.

- In addition to thrombotic and thromboembolic risk, are there other safety issues that should be addressed within long-term or large Phase 4 studies?

The committee suggested that Phase 4 studies should investigate known and potential benefits and harm, including thrombotic/thromboembolic disease, breast, endometrial, and ovarian cancer, pelvic inflammatory disease, endometriosis, dysmenorrhea, and other disorders. However, most contended that venous thromboembolism represented the major risk.-summation from **Final Summary Minutes**

- Can labeling information be made more useful for counseling patients to better inform patients about the likely effectiveness, safety, and other "acceptability considerations" (e.g., that a reduction in scheduled bleeding may be offset by an increase in unscheduled bleeding)?

The committee consensus is yes.-summation from **Final Summary Minutes**

- Would such information likely reduce discontinuation rates and improved actual product effectiveness?

The committee consensus is possibly. Studies are needed.-summation from **Final Summary Minutes**

- Should product labeling be modified to include pregnancy rates or safety data for specific subgroups when available?

The committee consensus is yes. Some suggest that a structured synopsis or abstract that clearly states efficacy, effectiveness, and proven side effects/complications is very important. The wording should be concise, clear-cut and understandable, in simple terminology, for example with absolute and attributable risks, not just odds ratios and confidence intervals.-summation from **Final Summary Minutes**

- How can labeling best communicate how to manage a situation where a patient misses pills?

The committee recommends following the World Health Organization recommendations on this issue.-summation from **Final Summary Minutes**

- Should potential secondary, non-contraceptive, benefits of hormonal contraceptives be discussed in labeling?

The committee took exception to the word "potential". The committee felt that only well-established, documented and replicated benefits should be included in the labeling, not unproven possible benefits. Labeling should identify the dosage for which benefits have been proven.

-summation from **Final Summary Minutes**

## CMC

Lybrel is an oral contraceptive that contains two drug substances: levonorgestrel and ethinyl estradiol. Levonorgestrel is contained in the drug product at 90 µg and ethinyl estradiol at 20µg.

The drug substances are manufactured by Schering and information is provided in DMFs 4178 and 1985. Complete information on levonorgestrel is contained in Schering's DMF # 4178. The DMF was reviewed for this NDA and found to be adequate. Complete

information on ethinyl estradiol is contained in Schering's DMF 1985. The most recent review of the DMF was done by R. Agarwal (Review # 8, dated 21-Nov-2005) and found adequate.

The drug product is a continuous-use oral contraceptive (no pill-free period). In the original application, the tablets were manufactured by [REDACTED]. Due to inadequate bridging of the clinical supplies manufactured by [REDACTED] method to the to-be-marketed tablets manufactured via [REDACTED], and the Sponsor's reluctance to perform a BE study for this change, the Sponsor opted to return to the [REDACTED] manufacturing method late in the review cycle. It was agreed that the revision was allowed, but supporting data arrived too late for review, so the NDA received an AE action. In the complete response dated 21-Aug-2006, the Sponsor submitted all required data for evaluation of the [REDACTED] manufacturing method. On 22-Dec-2006, the Sponsor submitted a major Amendment, changing the manufacturing method to the [REDACTED] method, submitting the required BE study to bridge [REDACTED] tablets and [REDACTED] tablets, and adequate stability data. Therefore, the to-be-marketed tablets will be manufactured according to the [REDACTED] method, which have been shown to be bioequivalent to the [REDACTED] clinical supply tablets.

b(4)

b(4)

The drug product is packaged in a Single Unit Dispenser which holds 28 active tablets containing 90µg levonorgestrel and 20µg ethinyl estradiol. For the Single Unit Dispenser, delivery of the pill is accomplished by squeezing the Dispenser to move the pill into an opening, where it is then dropped into the hand. Release of the Dispenser moves the next pill into place. The Sponsor has submitted 20 months of real-time stability data on tablets manufactured by the [REDACTED] method, and has requested 24 months of expiry based on this submitted data. Based on analysis of the submitted data, 24 months of expiry can be granted. Tablets are to be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F), [REDACTED].

b(4)

The Sponsor submitted two comparability protocols for post-approval changes in the original application and two additional comparability protocols in the 22-Dec-2006 Amendment:

- Comparability Protocol for Packaging of the Single Unit Dispenser
- Comparability Protocol for the Replacement or Deletion of Montanic Ester Wax
- Comparability Protocol for Foil-Based Component Interchangeability
- Comparability Protocol for Blister Films Interchangeability

The Montanic Ester Wax protocol requests a supplement category of CBE-30, while the packaging/packaging component protocols request a category of Annual Report. All four comparability protocols can be approved.

Because of submission of the December 22, 2006 Amendment changing to the [REDACTED] method and the adequate BE study comparing the [REDACTED] tablets, evaluation of the NDA was based on [REDACTED]

b(4)

the data used to support the \_\_\_\_\_ process. The Sponsor has demonstrated that the manufacturing process is robust and the release specifications adequately control the quality of the drug product.

b(4)

This NDA can be APPROVED from the CMC standpoint.

### OCPB

Submission s-042 is part of a second review cycle for NDA 21-864. This submission contains the results of the bioequivalence study under Protocol 0858A2-108-US. Lybrel™ tablets (LNG 90 µg/EE 20 µg; Test Tablets) manufactured using the \_\_\_\_\_ equipment were bioequivalent to Lybrel™ tablets (LNG 90 µg/EE 20 µg; Reference Tablets) manufactured using a \_\_\_\_\_ procedure. The ratio of geometric means for Cmax, AUCt and AUC0→∞ values were within the 80-125 goal post for BE for both LNG and EE (Table 1).

b(4)

There are no clinical pharmacology issues

### Pharmacology and Toxicology

A December 22, 2006 amendment was filed to address CMC issues for the continuous use contraceptive Lybrel™. There were no new nonclinical studies submitted for this amendment. Based on previously submitted nonclinical data for levonorgestrel (LNG) and ethiny estradiol (EE) from a Pharmacology/Toxicology perspective the LNG 90 µg/EE 20 µg dosage in the continuous use regimen can be approved.

### Conclusions:

Even after the contributions made with the discussions at the Hormone Contraceptives General AC, I remain concerned that an acceptable level of efficacy (in my opinion) was not demonstrated with the Lybrel™ application. In retrospect, the problem with applying the discussions of the General AC to this specific product is that there were a lot of discussions of options for moving forward with hormone contraceptive product development (particularly with trial design) without much advice as to the details. The decision for this product has to be based on the agreements, understandings and standards existing at the time the studies (primarily Study 0858A2-313-NA) were planned, conducted and filed with the Agency. Much of the AC discussion related to concepts with comparative trials and not historically-controlled trials as was the primary clinical study presented in this application. The committee failed to provide the Division with a point estimate or upper bound of a 95% confidence interval that it believed would establish efficacy. Instead it opted to advise that acceptability of product efficacy be considered on an individual basis; with the implication that this could be a moving target depending on whether a drug product offered other benefits. I will come back to this point later in this section of my review. Taken on an individual basis of the information presented in this application, it is still my belief that the failure rates for this drug product, whether assessed as the Pearl Index or Life Table method in "all users" or "perfect

users”, are unacceptably high in the population of American (North American) women who are equal to or less than 35 years of age. The assessment of the acceptability of this failure rate was based on comparison to a Pearl Index of 2 or less (the limit to the failure rate and the standard by which the Division has judged hormone contraceptives in the past). There were several references by AC committee members to this standard as being an arbitrary limit. This value very well may have been arbitrarily chosen. The discussions leading up to the acceptance of the limit of 1.5 and then 2.0 preceded my time with the Agency and documentation for these limits are available only in internal Agency documents. Nevertheless, if these limits were arbitrarily chosen they have withstood the test of time. With few exceptions (in fact, only 2 exceptions), all of the oral contraceptive products approved by the Agency have had a Pearl Index of less than or equal to 2. The literature has represented oral contraceptive drug products as highly effective with failure rates of 1 - 2% (not greater than 2 %). Likewise, the FDA in its literature aimed at educating the American consumer, lists the failure rates of oral contraceptives as 1 - 2%. I would argue that the 2% limit on the failure rate that the public has been educated to expect (the same failure rate assumed at the onset of the development of this product) be the limit that this product is judged by and not some newly created and individually-decided “arbitrary” limit that has no supportive science to uphold it.

“User failure” rates tend to be increased (relative to those seen in a clinical trial) once products are used in the “real world”. The reader is referred to Table 9-2 in Hatcher et al. Contraceptive Technology-18<sup>th</sup> revised edition which lists perfect use as 0.3% and typical use as 8%. Thus, the concern for this product, with at best marginal efficacy (and at worst scenario poor efficacy) relative to the efficacy demonstrated in the clinical trials for most of the approved oral contraceptive drug products (Pearl Index  $\leq 2$ ), is that once Lybrel™ is in general use the failure rates can be expected to be even worse. The same can be said for any contraceptive drug product, because efficacy in a clinical trial is usually as good as it gets. The point is that marginal or bad efficacy in a clinical trial becomes even worse in general use. This reviewer’s assessment of the efficacy of Lybrel™ remains unchanged. Unlike many of the reproductive drug products for which I perform the function as secondary reviewer, the consequence of failure of oral contraceptives is not simply one of inconvenience or symptomatic discomfort. An unintended pregnancy could pose a significant health risk to the mother and, if that mother is unprepared financially and emotionally for pregnancy, child-bearing and child rearing, an undue personal and societal burden that is of long-term (18-21 years) duration.

While no drug product or procedure can promise 100% efficacy, it is the expectation of women who take oral contraceptives that these products provide the highest level of efficacy and do what they purport to do, which is to prevent pregnancy. Based on the failure rates demonstrated in the U.S. clinical trial, Study 0858A2-313-NA, it is this reviewer’s belief that in the population for which it will be marketed, women in the U.S. desiring contraception, Lybrel™ will provide less than optimal contraception. Clearly there are those, both within this Agency and out (including members of the AC), who will argue that “the market” should decide about this product and if it is a poor product

and does not deliver with respect to efficacy, it will not be used by physicians and patients (this opinion was expressed by at least a few AC member). The Latin phrase “caveat emptor” was used several times. In my view, the problem with these arguments for this class of drug products (hormonal contraceptives) is that there is an inherent lag time before “the market” can catch on that there is a problem with marginal or poor contraceptive “effectiveness” in an approved product (i.e. the trial and error period before the physician realizes that his or her patients are getting pregnant on a particular drug and that their experience with this product is not isolated). In the interim, some women will be harmed with unintended pregnancies.

The Chair of the General Reproductive AC summed up that an acceptable pregnancy rate depends on safety and potential biologically plausible benefits. I think no one would argue with the former and all of the reviewers of this product have taken the safety profile (which is more than reasonable) into consideration. It is the latter concept that I am having some difficulty with. Approving a product with lesser efficacy based on a **potential biologically plausible benefit**. I think that Dr. Peterson’s caution, that I will paraphrase as when one starts to get into the realm of theory a whole cascade of potential problems may be initiated, is an excellent piece of advice. That being said, I can not identify a benefit with this product that would encourage me to recommend that the Agency accept a lower level of efficacy. Even the purported benefit of sustained amenorrhea was not supported in the trials for the 41.3% of the subjects who were not amenorrheic by pill pack 13 (or 1 year of use). No evidence of other non-contraceptive benefit was presented in the NDA.

Yes, I completely and fervently agree with the sentiments echoed by many of the AC members that for the drug products that are approved, we must provide in the label complete information in an easily understandable form. But we can not use the label to do our job to make sure the product is effective, as well as safe, before it is made available to the American public. The average patient visit to discuss contraception is on the order of 15 min or less. This is not enough time to do what would take weeks, if not months, in our hands to compare the efficacy and safety, benefits and risks of one pill vs. another. It seems to me that to ask women to make such high level comparisons and decisions in such a short time for an indication, such as contraception, where the potential consequence of a misguided decision is so high, is not only unfair to them, it may be doing them a disservice. Let me be clear on one point, this product will work well for some women. However, that population of women was not clearly and absolutely defined in the clinical trial. It is my belief based on the information that was available, especially comparing across study the results from Study 0858A2-313-NA (US) to Study 0858A2-315-EU (Europe), that women with low weight and body mass index will likely do fine with this product from both a contraceptive and unanticipated bleeding and/or spotting standpoint. However, this population description of women, which does not represent the majority of women in this country, will likely do equally as well with one of the myriad of other prior-approved hormonal oral and non-oral contraceptive products. I would argue that one subset of women should not have to risk unintended pregnancy to provide another set of women with an additional option.

I believe that the FDA should continue to encourage low dose products and products with alternative dosing regimes that are first both efficacious and safe, and secondly likely (meaning there is some data to support this) to provide consumers with non-contraceptive benefits and alternatives. I do not believe that Lybrel™ is such a product.

This reviewer can not in all good conscience recommend Approval of Lybrel™. In my opinion, to do so is to recommend a drug product that functions marginally for its intended indication of prevention of pregnancy in the population intended, that being American women at risk for pregnancy. Dr. Anita Nelson, representing the American College of Obstetricians and Gynecologist (The organization of Board-Certified physicians dedicated to women's reproductive health), stated that efficacy (in contraception) and safety should be the only basis for product approval. I echo that sentiment. I concur with the primary Medical Officer's recommendation that Lybrel™ not be approved.

In the *likely* event that it is decided at a higher regulatory decision making level that this drug product will be approved, then I can only hope that the label will be (as the AC committee has requested) fully informative and will provide the Pearl Index and Life Table failure rates reflective of all users (use failures and method failures) as well as "perfect users" (method failures) as determined during the medical officer and statistical review process. Further, there should be a caution to physician and patient that this drug product must be taken not only *every day* but at the *same time of day*. Finally, as the intent of this product was to provide sustained amenorrhea to women relying on it for contraception, the label should be honest in its depiction of the expected rates of cumulative amenorrhea of 58.3% (95% confidence interval 54.7, 61.8) at the 13<sup>th</sup> pill package of use and rates of unexpected/unanticipated bleeding and/or spotting. The label (dated May 15, 2007) recommended by the Clinical and Statistical reviewing team is attached to this review. This label may not be the final negotiated label with the Sponsor.

Post-Script (to the Reproductive Health AC and this Review):

The one unanimous and clearly unambiguous piece of advice delivered by the General Hormone Contraceptive AC was that in moving forward, the Division should ask for an active comparative trial as the basis for approval of hormone contraceptives. I believe that a blinded (perhaps even double-dummy as suggested by the Industry representative) does offer the most objective way of looking at these drug products. As with any proposal there are positives and negatives associated with this approach and the devil, as always, is in the details. The committee did not offer specific advice as to the hormone or oral contraceptive product to be chosen as the comparator and it refused to provide the Agency with a delta (or a clinically meaningful difference) by which the new product could be measured against the comparator. The choice of a comparator with lower efficacy and a wide delta will inevitably lead to the creep downward in efficacy that the Clinical Reviewing Team and at least several AC members expressed concern about. Further, the use of comparator trials would not provide the true Pearl Index or Life Table failure rate that the AC expressed should be in the label for any product. A solution to

this and the problem with creep would be to choose a comparator with a low Pearl Index or Life Table failure rate (there is at least one recently approved 35 mcg oral contraceptive with a Pearl Index less than 1) and apply not a wide delta (as expressed by some committee members) but a very tight delta. Another approach would be to satisfy both a point estimate and delta requirement. In any event, I would urge the Division, in moving forward, to take Dr. Gillen's offer to help the Agency in its review of the wealth of data on oral contraceptives from historical trials. Such a review will help the Agency look at the variability and determine a delta based on this extensive in-house data-bank and should eliminate what some have called "arbitrary" choice.

Shelley R. Slaughter, MD PhD  
Medical Officer Team Leader for NDA 21-864

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