UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PACIRA PHARMACEUTICALS, INC., DR. LOREN J. HARRIS, and DR. JOSEPH W. BELL, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION; UNITED STATES OF AMERICA; DR. STEPHEN OSTROFF, in his official capacity as Acting Commissioner of Food and Drugs; UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES; and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	Civil Action No. 1:15-cv-07055-RA

Declaration of Lee-Jen Wei, Ph.D.

I, Lee-Jen Wei, Ph.D., declare as follows:

1. I received a Ph.D. in Statistics in 1975 from the University of Wisconsin. I have been a tenured professor of biostatistics at Harvard University since 1991 and was a professor of biostatistical science and computational biology at Dana-Farber Cancer Institute, Harvard Medical School, between 1997 and 2012. I was the scientific director for the Program of Quantitative Sciences for Pharmaceutical Medicine at Harvard School of Public Health and the co-director of the bioinformatics core at Harvard School of Public Health from 2003 to 2007. From 2003 to 2004, I served as the acting chair of the department of biostatistics at Harvard

University. I was a tenured full professor of biostatistics and statistics at University of Wisconsin, University of Michigan, and George Washington University from 1982 to 1991.

2. Throughout my career, I have been intimately involved in the design, monitoring, and evaluation of clinical trials. I have served on numerous Data and Safety Monitoring Boards ("DSMBs") for clinical trials and have extensive experience in the evaluation of efficacy and adverse event data from clinical studies. Since 2004, I have been actively involved in clinical research of pain medications, developing and publishing a number of new quantitative methods for analyzing data readily applicable to analgesic drug development.

3. My scholarly writings include over 150 articles in peer-reviewed journals. I am responsible for developing numerous novel statistical methods for designing, monitoring, and analyzing clinical studies, survival analyses, and meta-analyses. Many of these methods have been included in the most commonly used statistical software packages such as SAS, S-plus, and R. I have served on the editorial boards of a number of statistical journals and am an elected Fellow of the American Statistical Association and Institute of Mathematical Statistics. I am also a frequent reviewer for National Institutes of Health grants and contracts. I was named "Statistician of the Year" in 2007 by the Boston Chapter of the American Statistical Association. In 2009, I received the Wilks Medal from the American Statistical Association, one of the most prestigious awards in the field of statistics, for outstanding contributions to clinical trial methodological research.

4. My *curriculum vitae*, which includes a complete list of my publications, is attached hereto as Exhibit A.

5. I have been retained by attorneys for Pacira Pharmaceuticals, Inc. ("Pacira") and individual doctors to provide this declaration concerning the duration of effectiveness of Pacira's

product, EXPAREL (bupivacaine liposome injectable suspension), as demonstrated in the SKY0402-C-316 study in hemorrhoidectomy ("Study 316"). I am being compensated at my normal rate of $600 per hour for my time in this matter. In preparing this declaration, I consulted the (i) EXPAREL Prescribing Information ("PI," or "label"); (ii) the Integrated Summary of Efficacy for EXPAREL; (iii) the Statistical Analysis Plan for EXPAREL; (iv) raw data from Study 316, which supported FDA approval of EXPAREL; (v) the U.S. Food and Drug Administration's ("FDA") Amended Clinical Review, Statistical Review, and Cross-Discipline Team Leader Review of the EXPAREL New Drug Application ("NDA"); (vi) the Warning Letter issued by FDA to Pacira; and (vii) a sample of promotional materials for EXPAREL. This declaration summarizes my conclusions but does not discuss in detail all statistical methods and analyses I employed during my review of the data from Study 316; I am readily available to provide additional details if necessary. This declaration relies on my knowledge and experience evaluating the efficacy of analgesic medications as demonstrated in clinical trials.

I. BRIEF SUMMARY OF CONCLUSION

6. Based on my extensive review and analysis of documents related to and data from Study 316, I conclude that EXPAREL clearly demonstrated a reduction in pain intensity for up to 72 hours after surgery as compared to placebo. There are three bases for my conclusion.

7. *First*, Study 316 met its pre-specified primary endpoint. The primary endpoint in the study was the area under the curve of the cumulative pain intensity scores as measured for the first 72 hours following surgery. The results were highly statistically significant and indicate that EXPAREL was effective for up to 72 hours. This endpoint, which FDA informed Pacira was appropriate to assess EXPAREL's efficacy before Study 316 was initiated, has been used as

the primary endpoint in clinical trials of treatment efficacy evaluation for other analgesics because, as FDA itself has recognized, it reflects both magnitude *and* duration of effect.[1]

8. *Second*, FDA's *post hoc* analyses are not appropriate for use in casting doubt on the durability of EXPAREL's treatment effect. This is because, with respect to the *post hoc* analysis evaluating pain intensity scores at 10 separate points in time, Study 316 was not designed to detect differences in subject pain scores with respect to this *post hoc* endpoint at all 10 time points. For the *post hoc* analysis evaluating "pain-free" patients, FDA applied an unfair statistical adjustment to undercut its finding of a statistically significant difference between EXPAREL and placebo through 72 hours.

9. *Third*, EXPAREL's effectiveness up to 72 hours after surgery is well-supported by other analyses from the Study 316 data. The "time-to-event" analysis of one of the pre-specified secondary endpoints from Study 316, for example, which assessed the amount of time elapsed after surgery before subjects took "rescue medication" (*i.e.*, an opioid), clearly demonstrates EXPAREL's highly statistically significant advantage over placebo for the entire 72-hour follow-up period. It is important to note that although this outcome is a secondary endpoint of the study and the study was not designed to detect this treatment difference, the results show a highly statistically significant difference with respect to the durability of the treatment effect. That is, EXPAREL clearly postpones or eliminates the usage of rescue medication during the 72-hour time span. This event-time analysis procedure is a standard and conventional method to investigate temporal treatment effects. Additionally, FDA's own analysis of another endpoint, which considered the percentage of subjects who were "pain free" in the EXPAREL and placebo groups, similarly showed highly impressive results when

[1] Arthur Simone, Amended Clinical Review of EXPAREL 41 (Oct. 7, 2011) ("FDA Medical Review") (emphasis added).

evaluated according to conventional statistical methods. As a result, there is no doubt that EXPAREL has a sustained treatment benefit up to 72 hours.

II. BACKGROUND ON STUDY 316

10. Study 316 was a Phase 3, multicenter, randomized, double-blinded, placebo-controlled clinical trial to evaluate the safety and efficacy of EXPAREL for postsurgical analgesia in hemorrhoidectomy. The study included 189 subjects who were randomly assigned to receive a single dose of either EXPAREL or placebo, administered intraoperatively via local infiltration prior to wound closure. After surgery, subjects were permitted to take "rescue medication" in the form of 10mg intramuscular morphine every 4-6 hours upon request. Each study subject was asked to rate his or her pain intensity at rest at various points in time through 72 hours using a numeric rating scale from 0 ("no pain") to 10 ("worst possible pain") (each an "NRS-R pain intensity score").

11. The primary efficacy endpoint in Study 316 was the area under the curve ("AUC") of NRS-R pain intensity scores from 0 to 72 hours after surgery ("NRS-R AUC_{0-72}").[2] This endpoint provides an assessment of both the magnitude and duration of pain experienced by the study subjects.

12. In addition to the primary endpoint of NRS-R AUC_{0-72}, Study 316 evaluated the effect of EXPAREL on numerous secondary endpoints over the entire 72-hour duration of the study, including (i) the time to first use of rescue medication; (ii) the consumption of rescue medication; (iii) the percentage of subjects who required no rescue medication at all; and (iv) the percentage of subjects who were satisfied with their postoperative analgesia.[3]

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[2] The AUC is mathematically referred to as a definite integral. In this case, it is calculated by first creating a graph of (i) the pain scores on the vertical axis versus (ii) the time the pain scores were obtained on the horizontal axis. The AUC is equal to the area between the graph and the horizontal axis.

[3] FDA Medical Review at 80-81.

III. EXPAREL Demonstrated a Highly Statistically Significant Effect on Cumulative Pain Scores Over 72 Hours When Compared to Placebo

13. The type of endpoint used in Study 316 (AUC of NRS-R pain intensity scores) is an approximation of cumulative pain scores over the entire 72 hours and is an endpoint that has been used as the primary endpoint in clinical trials of efficacy for other analgesics.[4] Not surprisingly, FDA informed Pacira in 2006 that this was an acceptable endpoint for EXPAREL.[5] Further, FDA has acknowledged that "the [primary] endpoint [for Study 316] was chosen as it reflects both magnitude and duration of effect."[6]

14. There is no dispute that EXPAREL met the pre-specified primary efficacy endpoint of Study 316.[7] This means that the results demonstrated both that the NRS-R $AUC_{0\text{-}72}$ for patients receiving EXPAREL was lower than the NRS-R $AUC_{0\text{-}72}$ for patients receiving placebo (*i.e.*, cumulative pain scores were lower for EXPAREL than for placebo) and that this reduction was associated with a high degree of statistical significance. A high degree of statistical significance means that the difference observed in Study 316 between EXPAREL and placebo over 72 hours post-surgery is an actual difference and not simply a random occurrence.

15. For ease of reference, Table A, below, provides the primary endpoint results of Study 316 (*i.e.*, NRS-R $AUC_{0\text{-}72}$ for EXPAREL and placebo groups).

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[4] FDA Medical Review at 41.

[5] *Id.*

[6] *Id.* (emphasis added).

[7] *See, e.g.*, David Petullo, Statistical Review and Evaluation of EXPAREL 11 (Oct. 28, 2011) ("FDA Statistical Review") ("There was a statistically significant difference between treatment arms for the primary efficacy endpoint, AUC_{72}.").

Table A:

Study 316 AUC of NRS-R Pain Intensity Scores (Cumulative Pain Scores)

Time from 0 to:	Statistics	EXPAREL (n=94)	Placebo (n=93)
72 hours	Mean	141.6	202.3
	SD	100.58	104.14
	Median	137.0	186.0
	Minimum, Maximum	0, 491	22, 529
	Adjusted Mean (SE)	141.751 (10.6800)	202.484 (10.7343)
	Difference (SE)	-60.733 (15.0532)	
	95% CI for Difference	(-90.434, -31.033)	
	P-value	<0.0001	

16. As shown in Table A, through 72 hours of follow-up, the observed difference between the EXPAREL group NRS-R $AUC_{0\text{-}72}$ and the placebo group NRS-R $AUC_{0\text{-}72}$ is -60.733 in favor of EXPAREL with a 95% confidence interval of (-90.434, -31.033).[8] The 95% confidence interval means that, in layman's terms, one can conclude with 95% certainty that the true difference between EXPAREL and placebo in cumulative pain scores between the EXPAREL and placebo study arms is between -90 and -31. In other words, subjects treated with EXPAREL had cumulative pain scores as much as 90 points lower (where lower scores reflect less pain) than subjects in the placebo arm. Even in the "worst-case scenario" for EXPAREL in this study, patients treated with the drug experienced an approximate 31-point reduction in cumulative pain scores relative to the placebo over the entire 72-hour follow-up period.

17. Equally important to the analysis is the "p-value" in Table A ($p<0.0001$), which represents the statistical significance of the observed difference between the EXPAREL group and the placebo group. A p-value corresponds to the probability of observing a difference if in fact there is no difference. The lower the p-value, the less likely it is that the observed difference is the result of chance.

[8] Confidence intervals measure the precision of the point estimate.

18. In the case of the Study 316 primary endpoint, the observed difference was -60.7 with a p-value of <0.0001. Such an extremely small p-value demonstrates that this is a highly statistically significant result[9] and means that the observed difference was "real" and not simply a chance finding or random occurrence.

19. Indeed, FDA's statistical review team concurred that Study 316 met its primary endpoint and that multiple secondary endpoints demonstrated a treatment effect and supported a finding of efficacy.[10]

20. The clear conclusion from Study 316 is that it demonstrated that EXPAREL reduces AUC of NRS-R pain intensity scores (*i.e.*, cumulative pain intensity scores) as compared to placebo for up to 72 hours following surgery.

IV. FDA'S *POST HOC* ANALYSES ARE NOT APPROPRIATE TO CONTRADICT HIGHLY STATISTICALLY SIGNIFICANT EFFICACY RESULTS FROM A PRIMARY ENDPOINT

21. Despite the highly statistically significant results on a primary endpoint that FDA has used in the approval of other analgesic drugs and had stated was an acceptable endpoint for EXPAREL, the Agency's statisticians conducted two brand-new, *post hoc* analyses to dispute the results from the primary endpoint of Study 316. A *post hoc* analysis is a retrospective evaluation of data from a study; in other words, the analysis was not pre-specified in the study protocol even as a secondary endpoint.

22. FDA's first *post hoc* analysis evaluated the mean pain intensity scores of subjects in each study arm at each of 10 time points during the study from one hour to 72 hours following surgery. Rather than looking at the cumulative effect of EXPAREL on pain over the 72-hour recovery period, as specified in the study protocol, FDA's *post hoc* analysis compared

[9] In clinical studies, a p-value of <0.05 is generally considered to be statistically significant.

[10] Rigoberto Roca, Cross-Discipline Team Leader Review of EXPAREL 16-17 (Oct. 9, 2011) ("FDA Cross-Discipline Team Leader Review"); *see also* Medical Review at 91.

average pain levels between the EXPAREL and placebo groups at each of 10 fixed time points (1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours).

23. This analysis, according to FDA's statisticians, visually suggested that the pain intensity scores of subjects treated with EXPAREL are substantially lower than the placebo group for the first 24 hours after surgery, but that the differences are diminished from 24 hours to the end of the 72-hour follow-up period.

24. FDA also analyzed the percentage of "pain-free" subjects at 10 time points. While percentage of pain-free patients was a secondary endpoint in Study 316, FDA disagreed with the method Pacira used to determine "pain-free" status and instead used a *post hoc* method of assessing that status. On the basis of that unconventional method for analyzing critical trial data, FDA initially concluded that EXPAREL demonstrated a "significant treatment effect observed out to 72 hours post-dose."[11] Then, after applying an unfair and unconventional statistical adjustment, *see infra* ¶¶ 43-44, FDA's statistical team concluded that the difference between EXPAREL and placebo extended only through 36 hours.

25. The Agency relied upon these analyses to call into question the significance of the primary endpoint of NRS-R $AUC_{0\text{-}72}$, ultimately concluding that the "benefit of EXPAREL after 24 hours post-surgery is unclear."[12] Because of this conclusion, FDA alleged in its Warning Letter to Pacira that it was "misleading" for the Company to state that EXPAREL provided "pain control that lasts for up to 72 hours."[13]

26. *Post hoc* analyses, however, are exploratory. Using one to contradict the results of a pre-specified, FDA-accepted, primary endpoint of cumulative pain scores at 72 hours is

[11] FDA Statistical Review at 11.
[12] *Id.* at 10.
[13] Warning Letter at 4.

simply not an appropriate statistical approach. A well-designed clinical trial has a well-defined primary endpoint in the protocol and the statistical methods to evaluate that endpoint are specified in advance in a statistical analysis plan. The primary endpoint is the key determinative factor in how to select the sufficient number of subjects to enroll in a study. The number of subjects in a study is critically important because it determines whether the study is statistically powerful enough to identify any true differences between the study drug and the placebo (*i.e.*, to ensure that any observed difference would not be due to a chance occurrence).

27. In this case, Study 316 was designed to detect the true difference in the AUC of pain scores through 72 hours after surgery, and the size of the study was selected on that basis.

28. Study 316 was *not* designed to detect the differences in subjects' pain intensity scores or "pain-free" status at 10 distinct points in time, where 20 total analyses would have been necessary (*i.e.*, one for the EXPAREL arm and one for the placebo arm for all 10 time points for mean pain intensity and "pain-free" endpoints).

29. An impractically large sample size would have been required for that purpose. In fact, for the study to have been statistically powerful enough to detect differences between the EXPAREL and placebo groups at each of those 10 points in time for just one of these *post hoc* analyses, the study would have required approximately 650 subjects in each study arm, for a total of 1300 subjects. An EXPAREL study of that size would have been impractically large; imposing such an infeasible requirement would have delayed delivery of a therapy to patients who desperately need an effective pain medication other than an opioid.

30. FDA's reliance on its own *post hoc* analyses to dispute the highly statistically significant results of the primary endpoint of cumulative pain scores at 72 hours, an endpoint that it deemed acceptable for use in evaluating EXPAREL and of the type that has been used in

studies of other analgesic drugs, is simply not appropriate. Furthermore, as described below, to the extent one looks beyond the primary endpoint to assess EXPAREL's durability of treatment effect, there are other, more informative statistical analyses suggesting a prolonged benefit of EXPAREL up to 72 hours after surgery, including FDA's own endpoint of "pain-free" patients.

V. THE DURABILITY OF EXPAREL'S TREATMENT EFFECT UP TO 72 HOURS IS FURTHER SUPPORTED BY SECONDARY ENDPOINTS FROM STUDY 316 AND FDA'S OWN ANALYSIS OF "PAIN-FREE" PATIENTS

31. In addition to the primary endpoint of cumulative pain scores over time (NRS-R $AUC_{0\text{-}72}$), Study 316 evaluated the effect of EXPAREL on numerous secondary endpoints.[14] The results from a number of these secondary endpoints demonstrated a statistically significant advantage of EXPAREL over placebo through 72 hours. Specifically, a lower percentage of patients treated with EXPAREL received *any* postoperative opioid rescue pain medication compared to placebo through 72 hours, patients with EXPAREL consumed less rescue medication over 72 hours than patients in the placebo group, and a greater percentage of patients treated with EXPAREL rated themselves as satisfied with their postoperative analgesia compared to placebo at 72 hours. These results further support the robustness of the primary endpoint and clearly demonstrate the sustained treatment benefit of EXPAREL for up to 72 hours. Indeed, FDA's statistical review team concluded that the primary endpoint in Study 316 "was supported by the analyses of various secondary endpoints such as percentage of patients that were pain free and time to first use of rescue medication."[15]

32. In light of the highly statistically significant results on Study 316's primary endpoint, and other supportive data demonstrating EXPAREL's prolonged treatment effect, it is unfair for FDA to focus narrowly on *post hoc* analyses of its own choosing to claim that

[14] Over 30 secondary endpoints were evaluated in Study 316. FDA Medical Review at 44.

[15] FDA Statistical Review at 19; FDA Medical Review at 80-81.

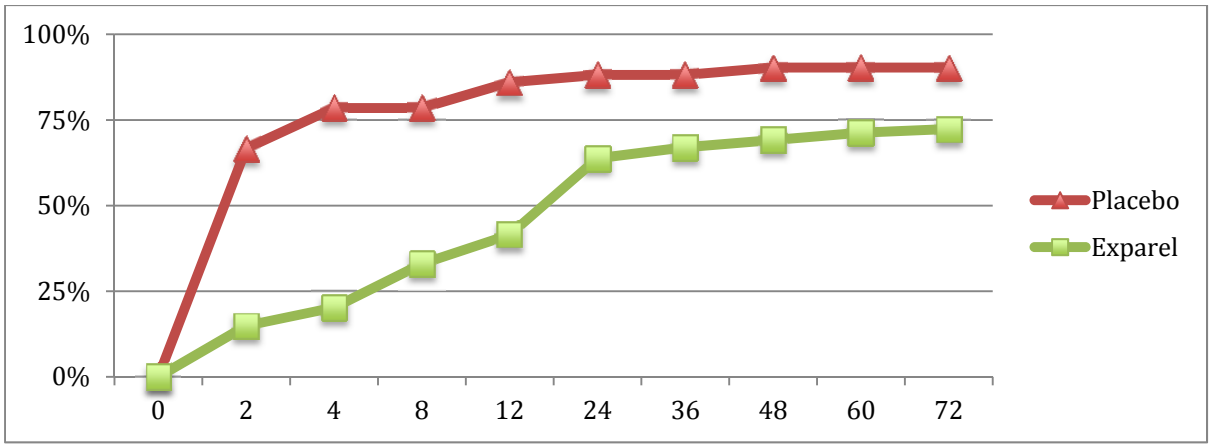
EXPAREL controls pain only for 24 hours. Doing so does not provide the full picture of results from Study 316. Below, I will describe a time-to-event analysis, one of the pre-specified secondary endpoints in Study 316, which is particularly revealing of EXPAREL's long-lasting benefit. I will also show—using FDA's own analysis—how EXPAREL demonstrated highly statistically significant totality of evidence with respect to patients who were "pain free" during the 72-hour follow-up period.

33. One of the most informative ways to assess durability of a treatment effect is to measure the time elapsed until a meaningful event occurs. This is called "time-to-event" analysis. Study 316 included such a time-to-event analysis as a pre-specified secondary endpoint. That endpoint assessed the amount of time elapsed after surgery before subjects took rescue medication. First use of rescue medication is a clinically meaningful "event" to analyze because it approximates the length of time during which a patient's pain is controlled. This secondary endpoint provides additional evidence indicating that the treatment effect of EXPAREL lasts for up to 72 hours. That is, we can use such an endpoint to assess how effective EXPAREL is in helping a typical patient postpone or eliminate rescue medication during the 72-hour follow-up time.

34. Figure A, below, shows two cumulative incidence curves representing the time to first use of rescue medication. The vertical line (Y-axis) is the percentage of patients starting use of rescue medication and the horizontal line (X-axis) is the time in hours. The curve with triangle symbol represents the placebo arm in Study 316, and the curve with circle symbol represents the EXPAREL arm. Note that the curve for the placebo arm is always above the curve for the EXPAREL arm for the full duration of the study. This means that EXPAREL is

uniformly better than the placebo over the entire 72 hours with respect to the time to first use of rescue medication.

Figure A: Time to First Use of Rescue Medication in Study 316 – Full Analysis Set



35. If we use the standard log-rank test in the literature for determining whether two underlying incidence curves are identical to each other for the entire patient population, the p-value is 0.00000000004. An alternate test statistic, the Wilcoxon test, yields a p-value of 0.000000000000005. Both of these results are exceptionally statistically significant and strongly demonstrate that the treatment benefit observed is not by chance, but rather reflects a true difference in the treatments over the entire 72-hour period.

36. Moreover, to quantify the prolonged treatment benefit from EXPAREL, we calculate the hazard ratio estimate (EXPAREL vs. placebo), which is 0.35 with a 95% confidence interval of (0.25, 0.49). That is, EXPAREL reduces the patient's hazard for initiating rescue medication by 65% (1 – 0.35 = 0.65) relative to the placebo on average over the entire 72 hours after surgery, an extremely impressive sustained treatment benefit.

37. Furthermore, at 72 hours after surgery, there remains a sizeable difference between the two curves (72% EXPAREL vs. 90% placebo). Put another way, only 10% of placebo patients required no rescue pain medication for the entire 72-hour period after surgery.

Nearly *three times* as many EXPAREL patients (28%) required no rescue medication at 72 hours. This difference was also highly statistically significant (p=0.0007). The fact that so many EXPAREL patients required no rescue pain medication for 72 hours after surgery further indicates that EXPAREL exerts a substantial analgesic effect for up to 72 hours.

38. This kind of time-to-event analysis is a standard and conventional way to examine the temporal profile of a treatment difference. And as demonstrated above, the results of the analysis make clear that EXPAREL has a significant treatment effect over placebo over the entire 72-hour period.

39. Turning to FDA's analysis of "pain-free" patients, that analysis—when evaluated with appropriate statistical methods as I will describe—shows that EXPAREL is effective over the 72-hour period after surgery.

40. FDA's endpoint analyzed the percentage of "pain-free" subjects at 10 time points, with "pain-free" subjects defined as those having a pain score of <2 who had not taken rescue medication. The results of this analysis are provided in Table B, below.

Table B: Percentage of Subjects that were "Pain Free" in Study 316

Treatment	Percentage of patients who were pain free and who had not taken rescue medication prior to that time point									
	1	2	4	8	12	24	36	48	60	72 hrs
Placebo	9	4	2	2	3	6	8	8	6	5
EXPAREL	48	45	46	39	30	23	24	20	17	16
p-value	*	*	*	*	*	0.001	0.002	0.01	0.02	0.02

* p-value <0.0001 (Chi-square test)

41. Notice that over the entire 72-hour follow-up period, the percentage of subjects who are pain-free is always higher for EXPAREL than for the placebo group. Even at the 72-hour mark, the final study observation point, the likelihood of being pain-free is tripled when

using EXPAREL compared to placebo (5% of placebo patients compared to 16% of EXPAREL patients).

42. Moreover, the p-values are less than 0.05 at all points in time. This is the conventional error rate for determining statistical significance in clinical studies, and it indicates that the observed differences in this analysis are "true" differences and are not chance findings. The FDA statisticians in fact initially concluded on the basis of this analysis that "there was a significant treatment effect observed [for EXPAREL] out to 72 hours post-dose . . . ."[16] That conclusion is correct. There should be no dispute about the efficacy of EXPAREL over the entire 72-hour follow-up period after surgery.

43. The FDA statisticians subsequently backed away from this conclusion, however, claiming that the method of controlling for Type 1 (false positive) error was not sufficiently rigorous because it did not allow for the multiple comparisons needed in light of the 10 time points captured in the analysis.[17] Applying a method known as the Bonferroni adjustment, which used an error rate of 0.005 rather than the conventional rate of 0.05, the statistical review team concluded that statistical significance was demonstrated only to 36 hours after surgery.[18]

44. The FDA statisticians applied an unconventional criterion in their attempt to control Type I error, because Study 316 simply was not designed to detect the treatment effect of EXPAREL at 10 separate points in time at a conservative 0.005 threshold. For example, if FDA's claim is that the treatment can only be considered to be "successful" if all 10 tests are significant with a p-value < 0.005, then by definition, the probability that a random study will be "successful" is less than 0.5%, far less than the conventionally accepted 5% ($p<0.05$) threshold.

[16] FDA Statistical Review at 11.
[17] *Id.*
[18] *Id.*

45. A more standard and conventional statistical procedure to analyze the data in Table B is to use the Cochran-Mantel-Haenszel method to combine all the data across the 72-hour time span. This creates a global outcome that reflects the totality of evidence across these 10 different analysis times. We may calculate the Cochran-Mantel-Haenszel odds ratio, stratified by analysis time, as a way to combine these 10 separate, dependent 2x2 tables. Using this procedure, we estimate a combined odds ratio of 7.7 for the effectiveness of EXPAREL relative to placebo, indicating that globally, across the 72 hours after surgery, subjects treated with EXPAREL have 7-fold greater odds of being pain-free without any use of rescue medication.

46. Because the subject outcomes at each of the 10 analysis times are not independent of one another, furthermore, we should employ a permutation test in order to calculate a p-value to determine the statistical significance of this observed treatment difference. To do this, we randomly permute the treatment assignments of the 187 subjects in Study 316 a large number of times, and for each permutation, we calculate the resulting Cochran-Mantel-Haenszel chi-square test statistic. Then we compare our observed test statistic to those that result from each random permutation.

47. For the present case, I conducted 5000 permutations to create 5000 randomly generated data sets from the 187 subjects in the study. None of the Cochran-Mantel-Haenszel test statistics associated with any of the 5000 data sets was as extreme as the one from the observed data from Study 316. This method leads to a p-value of $p<0.0002$, indicating that such differences between the EXPAREL and placebo treatment arms are extremely unlikely to occur unless there was a true difference between the therapies. Put another way, EXPAREL clearly showed a highly statistically significant advantage over placebo in pain-free subjects at all time

points, up to and including 72 hours after surgery with a conventional and standard statistical procedure for totality of evidence. This is the case even though Study 316 was not powered to show such a difference; in other words, due to the sample size of the study, we would not expect to see any statistically significant results across these 10 time points, especially not results that are so impressive.

VI. CONCLUSION

48. In sum, my review of the Study 316 data leaves me with no doubt that EXPAREL demonstrated a sustained treatment effect for up to 72 hours after surgery. EXPAREL showed a highly statistically significant advantage over placebo with respect to the primary endpoint of subjects' cumulative pain scores over the entire follow-up period. For the reasons described above, FDA's *post hoc* analyses are inappropriate to discredit these extremely impressive results on the primary endpoint. Furthermore, multiple other indicators provide additional support for the conclusion that EXPAREL's ability to control pain is long-lasting—in particular, the time to first use of rescue medication and FDA's own analysis of the percentage of patients who remained pain-free throughout the 72-hour follow-up period. As a result, FDA's allegations in the Warning Letter related to Pacira's "misleading" promotion of the 72-hour pain control are not justifiable.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge, information, and belief.

This Declaration was executed on September 8, 2015.

Lee-Jen Wei, Ph.D.