UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YOUNG, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION, UNITED STATES OF AMERICA, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	15 Civ. 3588 (PAE) ECF Case

DECLARATION OF CURTIS ROSEBRAUGH

I, Curtis Rosebraugh, M.D., M.P.H., hereby declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the following is true and correct to the best of my knowledge, information, and belief:

1. I am the Director of the Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am a board-certified Internist, and I have been with the Agency for approximately fifteen years. For the last ten years, I have served as Deputy Director, Acting Director, and Director of the Office of Drug Evaluation II, in which the Division of Metabolism and Endocrinology Products resides. That Division is responsible for reviewing and approving, among other things, new drug applications for drugs intended for the prevention and treatment of conditions relating to hyperlipidemia, which refers to elevated levels of lipids in the blood.

Drugs that fall into this class include Trilipix, Niaspan, Lovaza, and Vascepa. I have also held the positions of Deputy Director of Over-the-Counter Drug Products and Senior Medical Reviewer in the Division of Pulmonary and Allergy Drug Products in FDA's CDER. I received my medical degree from the University of Kansas School of Medicine, my master's degree in public health from The Johns Hopkins School of Public Health, and my undergraduate degree in pharmacy from the University of Kansas School of Pharmacy. I have held teaching appointments at University of Texas Medical Branch and University of Kansas Medical Center.

2. In these capacities, I am familiar with the steps FDA has taken to ensure that the labeling for triglyceride-lowering drug products reflects the most accurate and up-to-date scientific information regarding the relationship between drug-induced lowering of triglyceride levels and reducing the risk of cardiovascular events in patients on statin therapy. More specifically, I am familiar with FDA's decisions to remove indications related to statin co-administration from the labeling of Trilipix (fenofibric acid) and Niaspan (niacin extended-release) and to remove data and information about a triglyceride-lowering trial in statin-treated patients from the Clinical Studies section of the labeling for Lovaza (omega-3 acid ethyl esters). I am also familiar with the regulatory history for Vascepa (omega-3 acid eicosapentaenoic acid), which is accurately set forth in the June 5 letter from FDA to Amarin Pharma, Inc. ("Amarin").

3. In this declaration, I describe the approvals for Trilipix, Niaspan, Lovaza, and Vascepa, certain cardiovascular outcomes trials that are relevant to the labeling and approvals for these products, and steps FDA has taken and continues to take to ensure that healthcare professionals have information reflecting the best and most current scientific data about the lack of evidence to support the conclusion that decreasing triglyceride levels with a drug further reduces the risk of cardiovascular events among patients on statin therapy.

Approvals for Trilipix, Niaspan, Lovaza, and Vascepa

4. Trilipix is a fenofibrate-based drug. FDA first approved Trilipix on December 15, 2008, for several indications, including the following indication for co-administration with a statin: "Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG [triglycerides] and increase HDL-C [high-density lipoprotein cholesterol] in patients with mixed dyslipidemia and CHD [coronary heart disease] or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C [low-density lipoprotein cholesterol] goal." 2013 Trilipix Labeling, attached hereto as Exhibit 1.

5. Niaspan is an extended-release formulation of niacin. FDA initially approved Niaspan on July 28, 1997, for five indications. In 2003, FDA approved a supplemental new drug application ("sNDA"), adding an indication for the use of Niaspan in combination with lovastatin for the treatment of primary hypercholesterolemia and mixed dyslipidemia. *See* 2003 Niaspan Letter, attached hereto as Exhibit 2. In 2009, FDA approved an sNDA revising the indication related to statin co-administration to include mention of simvastatin as well. As of March 2015, this indication read as follows: "NIASPAN in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate." 2013 Niaspan Labeling, attached hereto as Exhibit 3.

6. Lovaza is composed of omega-3-acid ethyl esters, and contains mostly the ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In 2004, FDA approved Lovaza (originally known as Omacor) as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride levels in adult patients. Subsequently, Lovaza's sponsor conducted a trial in simvastatin-treated patients with triglyceride levels between 200 and 499 mg/dL, and well-controlled low-density lipoprotein cholesterol ("LDL-C") levels, to investigate the effect of

Lovaza on lipid measurements such as non-HDL-cholesterol and triglycerides, after 8 weeks of Lovaza treatment. FDA determined that the data on reductions in triglyceride levels from the trial were not sufficient to support the approval of an indication for the reduction of non-HDL-cholesterol, triglycerides, and other lipid parameters in this population, but FDA approved labeling that summarized data and information about the trial in the Clinical Studies section. *See* 2007 Lovaza Letter (approving Lovaza's proposed labeling), attached hereto as Exhibit 4.

7. Vascepa is a purified ester of EPA derived from fish oil. *See* June 5 Letter and citations therein. FDA approved Vascepa in July 2012 as a drug to be used as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as trigylceride levels ≥500 mg/dL ("very high trigylceride levels"). The primary rationale for treating individuals with very high trigylceride levels is to reduce the risk of pancreatitis. Pursuant to a Special Protocol Assessment ("SPA") agreement with FDA, Amarin also conducted the "ANCHOR trial" to assess the effect of Vascepa on trigylceride levels in statin-treated patients with well-controlled LDL-C levels whose trigylceride levels remained high. In this context, changes in trigylceride levels were being used as a surrogate to predict lowering the risk of cardiovascular events. In February 2013, Amarin then sought FDA approval to market Vascepa for another use, namely to treat patients with trigylceride levels between 200 mg/dL and 499 mg/dL ("high trigylceride levels") who are already being treated with statins to lower cholesterol. The primary rationale for treating statin-treated patients with this range of trigylceride levels with a second drug is to further reduce the risk of cardiovascular events, such as cardiovascular morbidity or mortality, resulting from atherosclerotic cardiovascular disease.

ACCORD-Lipid Trial

8. In March 2010, the results from the ACCORD-Lipid trial were published online in the *New England Journal of Medicine*, attached hereto as Exhibit 5. The ACCORD-Lipid trial evaluated the effectiveness of fenofibrate. Specifically, the ACCORD-Lipid trial was designed to answer the following question: In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to increase HDL-C and lower triglyceride levels together with a statin to lower LDL-C reduce the rate of cardiovascular disease events compared with a strategy that uses a statin and a placebo?

9. Although there were favorable changes in lipids, including reductions in triglyceride levels, the ACCORD-Lipid trial failed to demonstrate a statistically significant reduction in major adverse cardiovascular events among individuals treated with fenofibrate and simvastatin compared with those treated with simvastatin alone. The active ingredient in Trilipix is the active metabolite of fenofibrate.

Trilipix and ACCORD-Lipid Advisory Committee

10. FDA convened an advisory committee on May 19, 2011, to discuss the results of the ACCORD-Lipid trial and their implications regarding the Trilipix labeling. The committee considered whether FDA should allow continued marketing of Trilipix's indication for co-administration with a statin without revision of the labeling, withdraw approval of the indication, or allow continued marketing of the indication with revision of the labeling to incorporate the principal findings from the ACCORD-Lipid trial. Three members voted to allow continued marketing of the indication without revision to the labeling; four members voted to withdraw approval of the indication for co-administration with a statin; and six members voted to allow continued marketing with a statin, but to revise the labeling to incorporate the principal findings

from ACCORD-Lipid. *See* 2011 Summary Minutes, attached hereto as Exhibit 6.

Trilipix Labeling Changes and Postmarketing Clinical Trial

11. In July 2011, based on the results of the ACCORD-Lipid trial, FDA notified the Trilipix sponsor that another postmarketing clinical trial would be required to evaluate the effect of Trilipix on the incidence of major adverse cardiovascular events in high-risk men and women at LDL-C goal on statin therapy, but with residually high triglycerides and low HDL-C. *See* 2011 AbbVie Letter, attached hereto as Exhibit 7. FDA also required changes to the Trilipix labeling. Under the heading "Important Limitations of Use," the following language was added: "Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus." The ACCORD-Lipid trial was one of the two trials referenced in this statement. *See* 2011 Trilipix Labeling, attached hereto as Exhibit 8. In addition, a description of the ACCORD-Lipid trial was added to the Warnings and Precautions section of labeling ("Mortality and Coronary Heart Disease Morbidity" subsection), and the Medication Guide was updated. *See* Exhibit 8.

12. FDA's decisions to require a postmarketing clinical trial and the labeling changes described above, rather than to remove the indication for statin co-administration, were informed by the majority opinion of the advisory committee, which did not recommend removal at that time. FDA's decisions were also informed by the fact that two other trials briefly described below (the AIM-HIGH trial and the HPS2-THRIVE trial) were well underway at the time and were expected to further inform the effect on cardiovascular outcomes of adding a second lipid-altering drug (specifically, trigylceride-lowering/HDL-C-raising drugs) to statin therapy.

AIM-HIGH Trial

13. In December 2011, the results of the AIM-HIGH trial were published in the *New England Journal of Medicine*, attached hereto as Exhibit 9. The AIM-HIGH trial tested the effectiveness of extended-release niacin in patients on simvastatin therapy. Specifically, the trial was designed to test the hypothesis that niacin added to optimal statin therapy will reduce the risk of cardiovascular events compared with statins alone in patients with atherosclerotic cardiovascular disease and atherogenic dyslipidemia.

14. The AIM-HIGH trial was terminated earlier than expected because a formal interim analysis demonstrated a lack of efficacy. The AIM-HIGH trial failed to demonstrate a cardiovascular benefit of adding extended-release niacin to simvastatin therapy in patients with atherosclerotic cardiovascular disease and atherogenic dyslipidemia. FDA did not pursue removal of the statin co-administration indication for Niaspan at that time because the results of the HPS2-THRIVE trial were forthcoming. As discussed further below, the HPS2-THRIVE trial also studied the cardiovascular effects of a niacin-containing product in statin-treated patients, but in a much larger population than the AIM-HIGH trial. The HPS2-THRIVE trial had the potential to provide valuable information to inform not only the potential benefits of niacin, but also the clinical benefits, if any, of modulating lipid/lipoprotein biomarkers other than LDL-C among statin-treated patients.

Niaspan Labeling Changes

15. Following review of the AIM-HIGH data, FDA updated the labeling for Niaspan. Results from the AIM-HIGH trial were added to the Warnings and Precautions and Adverse Reactions sections of labeling, and a new Limitation of Use was added. The letter approving the prior approval sNDA with the package insert is attached hereto as Exhibit 10. Specifically, the

following statement in the Limitations of Use was added to the Indications and Usage section of the Niaspan labeling:

> NIASPAN, at doses of 1,500-2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter *[see Warnings and Precautions (5.1)]*.

Exhibit 10. FDA considered the addition of the AIM-HIGH results to Niaspan's labeling to be adequate to inform physicians about the trial results, and FDA planned to evaluate whether additional labeling changes were necessary once the results from the HPS2-THRIVE trial were made available.

HPS2-THRIVE Trial

16. The results of the HPS2-THRIVE trial were presented publicly on March 9, 2013, at a meeting of the American College of Cardiology and then published in the *New England Journal of Medicine* on July 17, 2014, attached hereto as Exhibit 11. The HPS2-THRIVE trial was designed to assess the effects of adding an extended-release niacin formulation, in combination with the anti-flushing drug laropiprant, to an effective statin-based LDL-C-lowering treatment for high-risk patients with prior vascular disease.

17. The HPS2-THRIVE trial was expected to be a more definitive trial than the AIM-HIGH trial. The population of the HPS2-THRIVE trial was 25,673 patients, compared with the 3,414 patients in the AIM-HIGH trial. In general, in randomized controlled trials, having more patients in a trial makes it more likely that a difference between treatment groups (e.g., drug versus placebo) will be detected, if a difference truly exists. Like the AIM-HIGH trial, the HPS2-THRIVE trial failed to demonstrate clinical benefit from the addition of an extended-release niacin-containing product to effective LDL-C-lowering statin therapy among high-risk patients with prior cardiovascular disease.

The Vascepa Advisory Committee Meeting, the Rescission of the ANCHOR SPA Agreement, and FDA's Decision Not to Approve Amarin's sNDA

18. During the same timeframe in which the data from the cardiovascular outcomes trials became available, Amarin conducted and completed the ANCHOR trial. The ANCHOR trial was an adequate and well-controlled clinical trial designed to determine whether Vascepa lowers triglyceride levels in statin-treated patients with well-controlled LDL-C levels and high triglyceride levels. The results demonstrated a statistically significant reduction in triglyceride levels in the Vascepa groups compared with the placebo (mineral oil) groups. Based on the ANCHOR trial results, and following 50% enrollment of patients into Amarin's cardiovascular outcomes trial involving Vascepa ("the REDUCE-IT trial"), Amarin submitted a sNDA seeking approval for Vascepa as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo B (apolipoprotein B), LDL-C, TC (total cholesterol), and VLDL-C (very low-density lipoprotein cholesterol) in adult patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent.

19. On October 16, 2013, FDA consulted with an advisory committee to obtain outside expert advice regarding the experts' level of confidence that the ANCHOR results would translate into a reduction in cardiovascular risk among the target population. FDA also asked the committee whether Vascepa's effects in the target population were sufficient to grant approval for co-administration with statin therapy for treatment of patients similar to the ANCHOR population, prior to the availability of results from the REDUCE-IT trial. The REDUCE-IT trial is expected to provide evidence for whether or not adding Vascepa to statin therapy further reduces the risk for cardiovascular events among patients with high triglyceride levels. Among other things, the committee discussed the results of the ANCHOR trial and the results of the three aforementioned cardiovascular outcomes trials and their potential impact on Amarin's

pending sNDA for Vascepa. As noted in the summary minutes of the meeting, "panel members stated that the available data from recent clinical trials do not strongly support an expected cardiovascular outcome benefit from lipid changes similar to those observed with Vascepa treatment." 2013 Summary Minutes, attached hereto as Exhibit 12. There was substantial discussion that the rationale for use of Vascepa in this patient population was to impart a cardiovascular benefit, and the panel expressed their considered opinion that "there is uncertainty regarding the clinical benefits of the observed lipid changes." Exhibit 12. The committee voted 9 "no" and 2 "yes" on the question of whether Vascepa should be approved for this indication prior to the completion of the REDUCE-IT trial.

20. Following the advisory committee meeting, FDA's review division rescinded the ANCHOR SPA agreement. FDA's review division concluded that it no longer had sufficient confidence that a change in triglyceride levels is sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in statin-treated subjects with high trigylceride levels. FDA's review division denied Amarin's request for reconsideration, and the rescission decision was upheld during two subsequent levels of formal dispute resolution on the grounds that (1) no adequate and well-controlled trial has demonstrated a cardiovascular benefit resulting from drug-induced lowering of triglyceride levels in statin-treated patients, and (2) three recent clinical trials failed to show additional cardiovascular benefit of adding a non-statin drug to statin therapy, even though each drug had lowered triglyceride levels significantly in statin-treated patients.

21. Rescission of a SPA agreement is a rare occurrence. Of the approximately 1,000 SPA agreements entered into by FDA and sponsors of investigational new drug applications over the last seven years, only ten have been rescinded. The rarity of SPA agreement rescission

indicates that FDA does not take the rescission process lightly or without due consideration. FDA determined that it could not approve Amarin's sNDA in its current form because there are insufficient data to support lowering triglyceride levels as a surrogate for reducing cardiovascular risk in statin-treated patients with well-controlled LDL-C levels and high triglyceride levels. FDA advised Amarin that to obtain approval, it would need to provide evidence that Vascepa reduces the risk of major adverse cardiovascular events in patients at high risk for CVD, with high triglyceride levels and well-controlled LDL-C levels on statin therapy. FDA also told Amarin that it anticipated that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency. Amarin has committed to continuing the REDUCE-IT trial and has stated that it expects that the trial will be completed in 2017, with results expected to be available in 2018. *See* Compl. ¶ 67.

FDA's Removal of the Niaspan and Trilipix Statin Co-Administration Indications

22. The ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE trials all failed to demonstrate incremental cardiovascular benefit of a second lipid-altering drug (fenofibrate or formulations of niacin) when added to statin-treated patients with well-controlled LDL-C, despite favorable effects on biomarkers of cardiovascular risk (e.g., triglyceride levels and HDL-C levels). Based on the totality of these new data, FDA determined that the indications related to co-administration with statins should be removed from the labeling of Niaspan and Trilipix on the basis that the recent cardiovascular outcomes trials failed to support the previously held belief that the putatively favorable changes in lipid biomarkers induced by these drugs would lead to a reduction in cardiovascular disease risk in statin-treated patients. Accordingly, FDA revised the labeling for Niaspan and Trilipix to remove the indications related to statin co-administration. Consistent with the removal of this indication from the Trilipix labeling, FDA

also released the Trilipix sponsor from the requirement to conduct a post-marketing cardiovascular outcomes trial to evaluate the risk of major adverse cardiovascular events in patients treated with Trilipix when co-administered with statin therapy; such a trial had not been required of other fenofibrate sponsors, because no other fenofibrate product has an indication for co-administration with a statin. Copies of the current labeling for Niaspan and Trilipix are attached hereto as Exhibits 13–14.

23. FDA's revision of the labeling for these products to remove the indications for co-administration with a statin was based on the evolving nature of the available scientific data. At the time the statin co-administration indications for Niaspan and Trilipix were approved, available scientific evidence suggested that favorable changes in lipid parameters would translate to a reduction in cardiovascular risk. The statin co-administration indications for Niaspan and Trilipix were approved based on data demonstrating statistically significant changes in lipid parameters such as TG, HDL-C, and non-HDL-C beyond those achieved by taking a statin alone. But in all three cardiovascular outcomes trials discussed above, further lowering of triglycerides (as well as other putatively favorable lipid changes) failed to further reduce cardiovascular risk in patients already treated with a statin. Although elevated triglyceride levels are associated with adverse cardiovascular outcomes, a drug-induced change in a risk factor does not always result in the expected effect on clinical outcomes, and the best scientific data currently available have failed to demonstrate that drug-induced triglyceride lowering (with either Niaspan, an extended-release niacin, or fenofibrate) results in a reduction in cardiovascular risk in patients who are already on optimal statin therapy. FDA thus determined that the statin co-administration indications should be removed from the labeling for Niaspan and Trilipix.

FDA's Removal of Statin Co-Administration Data from the Lovaza Labeling

24. As mentioned above, FDA permitted inclusion of data and information in the Clinical Studies section of Lovaza's labeling about a trial that studied the effects of Lovaza on lipid measurements (such as triglycerides and non-HDL-C) in simvastatin-treated patients with triglyceride levels between 200 and 499 mg/dL, and well-controlled LDL-C levels. An indication was not granted based on this trial, however, because FDA determined that the reductions in triglyceride and non-HDL-C levels were not sufficient to support the approval of an indication. FDA later concluded that, in the absence of an approved indication for treatment of patients with high triglyceride levels despite statin therapy, it was not appropriate to continue to include data about the co-administration of Lovaza with a statin in this patient population in the Clinical Studies section of the Lovaza labeling. This conclusion was based on several reasons. First, the inclusion of non-indication-specific data and information other than for safety related reasons in the Clinical Studies section of the drug labeling is inconsistent with FDA's regulation, guidance, and policies. *See, e.g.*, 21 C.F.R.§ 201.57. Second, in patients on statin therapy, the published results of ACCORD-LIPID, AIM-HIGH, and HPS2-THRIVE raised substantial doubt regarding the clinical benefit of reducing triglyceride levels with a second lipid-altering drug intended for the purpose of reducing cardiovascular disease risk. Consequently, FDA no longer believes that the totality of the scientific evidence supports a conclusion that a drug-induced reduction in triglyceride levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Third, with respect to Lovaza, its NDA sponsor had not carried out any cardiovascular outcomes trials to establish such a benefit. For all these reasons, FDA asked the sponsor of the NDA for Lovaza to remove the content related to this trial from the Clinical Studies section, and revised labeling was approved shortly thereafter. *See* 2014 GSK Letter and

2014 Lovaza Labeling, attached hereto as Exhibits 15 and 16, respectively.

The JELIS Trial and Its Limitations

25. I understand that Plaintiffs allege that the JELIS trial results support a cardiovascular benefit from EPA therapy in the studied population. It is important to exercise caution in drawing such a conclusion from the published results of the JELIS trial. The results of the JELIS trial were published in the *Lancet* in March 2007, attached hereto as Exhibit 17. To give a brief summary of the JELIS trial, Japanese adults with elevated cholesterol levels with or without coronary artery disease were administered either EPA with a statin or statin alone. The primary endpoint of the trial was a major coronary event, defined as sudden cardiac death, fatal or nonfatal myocardial infarction, unstable angina, and coronary bypass surgery or angioplasty. There was a 5 percentage point difference between the groups in the relative changes in triglyceride levels from baseline to the last clinic visit. The 5-year cumulative rate of major coronary events was 2.9 percent in the EPA plus statin group and 3.5 percent in the statin-alone group, resulting in a statistically significant relative risk reduction of 19 percent. The breakdown of the individual components of the primary endpoint shows the strongest evidence of the treatment effect with EPA on unstable angina.

26. As part of its presentation to the advisory committee during the October 16, 2013, meeting, as well as when considering whether to rescind the SPA agreement for the ANCHOR trial, FDA reviewed the published results of the JELIS trial. FDA identified limitations to the design of the JELIS trial that affect the interpretation of the trial's results. First, the subjects in the JELIS trial were limited to Japanese adults receiving a low dose of statin therapy that may be considered inadequate in the United States. Second, the JELIS trial was an open-label trial. In such a trial, both researchers and participants know whether a participant is being administered

the drug or placebo. Having this knowledge can influence physician and patient behavior, such as the reporting of symptoms. Third, the main component of the primary endpoint in the JELIS trial was unstable angina, which is a more subjective endpoint than, for example, objective major adverse cardiovascular event endpoints (e.g., heart attack, stroke, or cardiovascular death). A subjective endpoint such as unstable angina may be particularly unreliable in an open-label trial where patients and physicians are making decisions regarding hospitalizations.

27. In addition to these design limitations, patients treated with EPA and statin achieved triglyceride levels that were only 5 percent lower, on average, than those achieved among the patients treated with statin alone; however, the reduction in cardiovascular risk was 19 percent. The large difference in magnitude between the triglyceride reduction and risk reduction suggests that the effects of EPA on triglycerides may not be responsible for, or predict, the observed differences in cardiovascular events between treatment groups in this trial. For all these reasons, CDER's review division determined, when considering whether to rescind the ANCHOR SPA agreement, that the results from the JELIS trial could not be used as support for or against the use of triglyceride levels as a surrogate for cardiovascular risk reduction. This conclusion was upheld during the dispute resolution process regarding the rescission of the ANCHOR SPA agreement.

PCSK9 Inhibitors Advisory Committee

28. FDA continues to base its approval decisions on the best and most current data regarding the relationship between lipid-lowering drugs and cardiovascular risk. For example, for more than the last two decades, FDA has used a reduction in LDL-C as a surrogate for cardiovascular risk reduction for several lipid-altering drugs to support traditional approval. Certainly, at least for statins, the validity of a reduction in LDL-C as a surrogate for reduced

cardiovascular risk has been confirmed through numerous randomized controlled trials involving multiple drugs in the class and a variety of patient populations with varying degrees of baseline risk and LDL-C values. On June 9 and 10, 2015, FDA convened advisory committee meetings to discuss the potential approval of two new drugs intended to reduce the risk of cardiovascular disease. These two drugs, both with the same mechanism of action, were shown to reduce LDL-C in multiple adequate and well-controlled trials, but their effects on cardiovascular outcomes remain under investigation in large, multi-year cardiovascular outcome trials. In recent years, other drugs that have had purportedly beneficial effects on various lipid biomarkers of cardiovascular risk (including but not limited to triglycerides) have not always been shown to reduce the risk of cardiovascular events when studied in dedicated cardiovascular outcomes trials. This contributed to FDA asking panel members to discuss whether lowering LDL-C remains a valid surrogate endpoint to predict cardiovascular benefit for the two drugs under discussion. Remarks were made by panelists that reduction of LDL-C lowering may not be an appropriate surrogate for clinical benefit in some of the broad patient populations that FDA has historically indicated for the use of LDL-C-lowering drugs. FDA will take the committee's remarks under advisement.

FDA's Efforts to Ensure that Physicians Have Updated Information About Trigylceride-Lowering Drugs

29. I understand that Amarin alleges the following in its Complaint: "Although, upon information and belief, while FDA has recently acted to remove the indication and labeling from these other triglyceride-lowering drugs concerning treatment of persistently high triglycerides, FDA has done little, if anything, to address the effect of permitting these drugs to be marketed for many years to healthcare professionals for treatment of adults with persistently high triglycerides." Compl. ¶ 10. This is a mischaracterization of FDA's efforts with respect to other

triglyceride-lowering drugs.

30. As described above, there have been two public advisory committee meetings discussing the recent cardiovascular outcomes trials and affected products. As the results from ACCORD-Lipid and AIM-HIGH became available, FDA required appropriate labeling changes for several triglyceride-lowering drugs, including Niaspan and Trilipix. Once the results from all three trials were available, and FDA determined that the collective scientific evidence showed that the reduction in triglyceride levels from a second lipid-altering drug has not been shown to provide an incremental benefit in reducing the risk of cardiovascular disease, FDA removed the indications from the labeling for Niaspan and Trilipix and the content from the Clinical Trials section of the Lovaza labeling. FDA also did not approve Amarin's supplemental new drug application seeking approval of Vascepa to lower high triglyceride levels in statin-treated patients with well-controlled LDL-C levels.[1]

31. FDA believes that these publicly available labeling changes and approval decisions

[1] In addition to FDA's actions, the results of these trials and their implications for clinical practice were published in a major medical journal, the *New England Journal of Medicine*; have been the subjects of numerous editorials and commentaries; and were mentioned in recent clinical practice guidelines. An example of such a clinical practice guideline is Stone NJ et al., "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults." *J Am Coll Cardiol* 2014; 63:2889-934. Examples of editorials and commentaries include: Warraich HJ et al. "Role for combination therapy in diabetic dyslipidemia." *Curr Cardiol Rep* 2015; 17:589; Ginsberg HN and Reyes-Soffer G. "Niacin: a long history, but a questionable future." *Curr Opin Lipidol* 2013;24:475-479; Brinton EA. "Search and rescue for hypotheses surviving AIM-HIGH, the niacin therapy earthquake: Still problematic after the primary publication." *J Clin Lipid* 2012;6:312-317; Nicholls SJ. "The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Trial: To Believe or Not to Believe?" *J Am Coll Cardiol* 2012; 59:2065-67; Sampson UK, et al. "Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges." *Curr Atheroscler Rep* 2012; 14:1-10; Goldfine AB, et al. "Fibrates in the treatment of dyslipidemias – time for a reassessment." *N Engl J Med* 2011; 365:481-4; Giugliano RP. "Niacin at 56 Years of Age – Time for an Early Retirement?" *N Engl J Med* 2011; 365:2318-2320.

reflect the most accurate and up-to-date scientific information about the lack of evidence demonstrating an incremental clinical benefit of Niaspan, Trilipix, Lovaza, and Vascepa on the risk of cardiovascular events in patients on statin therapy. The approval letters for these drugs, which include important information about the labeling changes, are all posted on FDA's website (Drugs@FDA: FDA Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). In addition, the public advisory committee meetings and the related meeting materials posted on FDA's website provide additional important information to the public about this topic. FDA also is in the process of taking additional steps consistent with the totality of the scientific evidence, which no longer supports the conclusion that a drug-induced reduction in triglyceride levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Thus, the agency has taken and continues to take appropriate steps to ensure that the most current and accurate information about triglyceride-lowering drugs and cardiovascular disease is publicly available.

32. Moreover, FDA has encouraged, and continues to encourage, sponsors of NDAs for triglyceride-lowering drugs to conduct the cardiovascular outcomes trials necessary to determine directly whether their products are effective in reducing the risk of cardiovascular events. Such trials also contribute important knowledge about lipid-altering drugs and cardiovascular risk. For example, the results of the REDUCE-IT trial will determine whether adding Vascepa to statin therapy further reduces the risk for cardiovascular events among patients with high triglyceride levels, and they also are expected to contribute significantly to the evolving body of science about lipid-altering drugs and cardiovascular risk and provide important information to physicians that will inform their decisions in prescribing these drugs. In addition, if such trials are successful and FDA ultimately approves the products for the indication studied, patients will

benefit from knowing that their daily pill burden is doing more than changing numbers on a laboratory report and that their therapy is safely and effectively reducing their risk of cardiovascular morbidity and mortality.

33. Contrary to Amarin's assertion, FDA's past actions — including convening two advisory committee meetings, removing indications from labeling, posting the materials from the meetings and the approval letters on FDA's website, and encouraging sponsors to conduct the necessary cardiovascular outcomes trials — do address the effects of permitting drugs like Niaspan, Trilipix, and Lovaza to be marketed to healthcare professionals for treatment of adults with high triglyceride levels. FDA's past and continued actions have made, and continue to make, healthcare professionals aware that there is insufficient evidence to support a conclusion that drug-induced decreases in triglyceride levels lead to a reduction in the risk of cardiovascular events in patients on statin therapy. Furthermore, FDA will continue to take additional steps as warranted in this area.

Executed on 6/22/2015.

Curtis Rosebraugh, M.D., M.P.H.