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 JANET WOODCOCK, M.D.

I, Janet Woodcock, M.D, 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 Center for Drug Evaluation and Research ("CDER"), United States Food and Drug Administration ("FDA"), United States Department of Health and Human Services ("HHS"). I joined FDA in 1986 and since then have been the CDER Director for a total of more than 17 years. I have also held the positions of Deputy Commissioner, Chief Medical Officer, and Director of the Office of Therapeutics Research and Review in FDA's Center for Biologics Evaluation and Research. I received my medical degree from Northwestern

University Medical School, and my undergraduate degree from Bucknell University. I have held teaching appointments at Pennsylvania State University and the University of California at San Francisco.

2. In these capacities, I am familiar with CDER's procedures for the review and approval of new drug applications including supplemental applications, and with FDA's regulations and policies relating to manufacturer communications regarding unapproved uses of approved products.

3. In this declaration, I describe, first, the public health interests advanced by the new drug approval requirements and certain misbranding provisions of the Federal Food, Drug, and Cosmetic Act ("FDCA"), particularly as they relate to firm-disseminated communications of scientific information regarding unapproved uses of their approved medical products. Second, I describe FDA's efforts to carefully tailor its policies to advance (and reconcile or balance) the varied and sometimes conflicting interests relating to these communications, and how FDA has applied this framework to Amarin's proposed speech about Vascepa. Third, I address why alternative approaches would not adequately protect the public health.

Government Interests in Protecting and Advancing the Public Health

4. The FDCA prohibits the introduction (or causing the introduction) into interstate commerce of a new drug that has not complied with requirements for approval (21 USC 331(d)), or any drug that is misbranded (21 USC 331(a), (b), (c), (g), (k)). These provisions and their implementing regulations prohibit introducing (or causing the introduction) into interstate commerce of a prescription drug that is intended for a use that has not been approved by FDA, even if that drug is approved for a different use. These provisions advance the substantial

government interests in increasing the availability of safe and effective therapies and preventing direct and indirect harm from products that are unsafe or ineffective. Before there was any effectiveness requirement, a wide variety of treatments were utilized that proved useless. A drug manufacturer now must show that a drug is safe and effective for each use of the product, and must define the appropriate conditions for that use, e.g., dosage, site of administration, contra-indications and warnings, before it is labeled and distributed for such use by the manufacturer.

5. A manufacturer's distribution of an approved product for an unapproved use has the potential to undermine the substantial public health interests underlying the premarket review and relevant misbranding provisions under the FDCA. If a firm could increase sales by disseminating scientific information regarding unapproved uses, the firm's incentive to comply with the FDA premarket review processes would be reduced because it could effectively market the product for an unapproved new use without expending the time and resources required for FDA approval. As a result, the public would be at risk of losing the significant public health protections advanced by the FDCA's new drug approval and relevant misbranding provisions as follows.

Motivating the Development of Robust Scientific Data on Safety and Efficacy

6. Congress mandated that firms gather data from rigorous scientific studies by establishing scientific evidentiary thresholds for approval. These requirements developed over time, partly in response to conduct by drug companies that led to public health tragedies and insufficient regulatory authority to prevent the harm from occurring. In enacting the 1962 Kefauver-Harris amendments to the FDCA (which first introduced an explicit efficacy requirement for drugs), Congress recognized that poorly conducted studies and the impressions

of practicing healthcare professionals do not provide adequate information to assess the risk/benefit profile of drugs necessary to protect and promote public health. Experience has also shown that even widespread acceptance of an unapproved use in the medical community is no guarantee that the medical product is safe or effective for that use. Despite this history demonstrating that conducting rigorous scientific studies of each new use of a medical product is necessary to protect the public health, the time and resources needed to conduct rigorous clinical research may be disincentives for firms to conduct these studies once their products have been approved for at least one use and thus can be legally placed into widespread distribution.

7. The current premarket approval process for each new use of a drug is designed to prevent harm by requiring firms to investigate and substantiate the safety and effectiveness of their drugs for each intended use before offering or distributing the products to the public for those intended uses. To receive FDA approval for the uses of their drugs, firms must generate the kind of data that supports a reliable conclusion that the reported results, particularly with regard to benefits, are causally related to the use of the drug or device, and not a result of other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation; firms must also show that the overall data and information supports use of the drug for each of its intended use(s). This requirement of scientific substantiation for approval of each intended use creates the impetus for firms to conduct studies that will allow the rigorous evaluation of the safety and effectiveness of a drug before it is widely used by the general public for that purpose. The alternative would be a system that would allow firms, which stand to profit from every sale of their product for any use, to encourage general public use of under-studied and unevaluated uses, with the potential for wide-scale public health tragedies and wasted public

and private health care dollars.

Timing of Review to Prevent Harm

8. Congress determined that FDA must review the safety and effectiveness of *each* intended use of certain medical products *before* the drug is introduced into interstate commerce for that use. Premarket review of both safety and effectiveness prevents harm; post-market remedies are often taken only after harm has occurred. Many drugs potentially have significant adverse side effects, and therefore may be deemed safe by FDA only with respect to particular uses that involve significant countervailing benefits. Further, beyond the direct harms sometimes caused by drugs, the lost opportunity to select an effective intervention against underlying disease (or the delayed diagnosis of a disease or condition in the context of diagnostic products) is itself a harm that often cannot be fully remedied after it is incurred.

9. The history of drug product regulation before 1962 demonstrates that exclusive reliance on post-marketing remedies, such as enforcement actions for false or misleading labeling, was inadequate to protect the public health. Those post-market remedies were not sufficient to deter some firms from making unsubstantiated or misleading claims to encourage use of their products and therefore could not prevent the often serious harm to health caused by the use of these products. Premarket approval for each intended use was necessary to prevent some firms from evading the drug approval requirements by obtaining approval for one use, then promoting the drug for other, unapproved uses without first demonstrating through the approval process that the drug was safe and effective for each new use.

10. In the context of emerging and developing scientific data, the ultimate relevance of information is often unknown. That is, one might truthfully summarize the data generated by a

study without being able to determine whether any inferences or conclusions drawn from the data would ultimately be shown to be correct. Where emerging and developing scientific data are not yet sufficiently complete or robust to determine safety and efficacy for an unapproved use, premarket review places the burden of uncertainty on the firm by restricting the firm's distribution of its product for that unapproved use. By contrast, in an enforcement action, the government typically bears the burden to prove that a communication is false or misleading, and in many cases, that action will occur only *after* the product has been purchased and used in reliance on that communication. Those differences in timing (premarket vs. post-market) and burden (firm vs. government) are particularly significant in light of the uncertainty that is often attendant to developing science. Placing the burden of uncertainty on the manufacturer limits patients' exposure to the risks associated with the use—an approach that advances the substantial government interest in preventing harm to the public health. By contrast, if the burden were on the government to establish that the information is false or misleading, effective relief might come too late to prevent harm to the public health. Thus, a framework under which firms may continue to distribute their drugs while also widely disseminating preliminary or unsubstantiated data, which may be misleading, about unapproved new uses would leave the public health at significant risk—even if the information is deemed scientific.

11. For example, erythropoiesis stimulating agents (ESAs) are approved for treatment of patients suffering from anemia due to chronic kidney disease (CKD) or chemotherapy use in patients with cancer. ESAs have been widely used in patients with CKD, not only for their labeled use of treating anemia in such patients, but also for the unapproved use of raising their hemoglobin to near-normal levels, above 12 g/dL, which was at one time believed to improve

symptoms and survival. ESAs were also widely used to treat anemia of cancer, regardless of whether or not a patient was undergoing chemotherapy, and at dosing schedules other than those approved by FDA. At least one of these unapproved uses—anemia of cancer—was listed as a "medically-accepted indication" in one of the compendia used to determine coverage for certain federal healthcare programs.

12. Subsequently, controlled trials of unapproved use of ESAs in CKD and patients with cancer revealed increased risks of cancer relapse, serious cardiovascular and thromboembolic events, and death. The widely held assumption by many in the medical community that increased hemoglobin and the larger doses of ESAs needed to attain higher hemoglobin levels would be beneficial proved thoroughly incorrect. Indeed, the larger doses of ESAs were lethal. FDA added a boxed warning to ESA products to warn about increased risk of death, serious cardiovascular events and stroke when administered to target higher hemoglobin levels. The warning also noted increased mortality and tumor progression or recurrence for patients with cancer treated with ESAs.

13. As another example, atypical antipsychotics are generally approved for schizophrenia and bipolar disorder. However, they have been commonly used to treat an unapproved indication of behavior problems in elderly patients with dementia. Subsequent controlled trials have revealed increased mortality resulting from this use, primarily resulting from deaths due to cardiovascular events and infectious disease. These products now bear a boxed warning noting the risks of using them to treat elderly patients with dementia.

Robust Review by Independent Scientific Agency

14. FDA premarket review also serves the purpose of assuring that safety and efficacy

are evaluated on a population basis under rigorous scientific standards by independent, scientifically expert reviewers. The history of public health tragedies caused by medical products demonstrates that there have been some unscrupulous players in the marketplace who have made deceptive or unsubstantiated and misleading claims about medical products. Even where a manufacturer is not deliberately manipulating the message, independent scientific review helps ensure that conclusions about the drug are adequately supported and unbiased. As a check against this potential for harm, Congress created FDA as a government agency with the appropriate scientific expertise and assigned it the task of independently reviewing applications for premarket approval under robust standards. FDA conducts this review to evaluate whether a drug is safe and effective for a particular use by comparing the expected therapeutic benefit against the risk associated with its use. In its premarket reviews, FDA evaluates, among other things, safety and efficacy data gathered and/or generated by the firm to verify that the standards for safety and efficacy have been met. In implementing these requirements for new drug applications, FDA requires the submission of, among other things, data and information on chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; human pharmacokinetics and toxicology; microbiology; clinical data; and statistical evaluations of clinical data. For each of these and other topics relevant to a particular application, FDA assigns review teams and primary reviewers who specialize in that scientific area to review that portion of the application and to generate a written evaluation. FDA then integrates all of the outcomes of these separate review activities to determine the appropriate outcome for the application. FDA's multi-disciplinary scientific review helps to identify what information is sufficiently evidence-based and to assess the degree of risk and likelihood of benefit from the use of a

medical product for a particular purpose.

15. This robust independent review protects the public health in several ways. If the industry were, instead, allowed to police itself, there would be no assurance that safety and efficacy would be evaluated under rigorous and impartial standards. Because firms have an underlying economic motivation that may skew their interpretation and presentation of the available scientific data, whether unintentionally or deliberately, the unbiased review by an independent scientific agency helps to ensure that any product approval is properly evidence based. This process protects the public from uses for which the benefits do not outweigh the risks, as well as from ineffective uses, which can harm individuals when the choice of an ineffective product causes them to delay or forego appropriate medical treatment. Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of scientific rigor and a thoroughness of evaluation that is not met by the more cursory examination of the peer review process, given the limited data typically available and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the breadth or scope of a journal article. When review is conducted by private entities, the review could also be influenced by industry-affiliation or other biases.

Diversion of Limited Healthcare Resources

16. In addition to the public health interests underlying and advanced by the premarket review provisions of the FDCA, communications regarding unapproved uses of approved products may lead to the diversion of limited healthcare resources. The expenditure of resources

on unsafe or ineffective products would itself be wasteful and may limit the availability of these resources for safe and effective treatments. In addition, to the extent there are adverse health consequences from the use of unsafe and/or ineffective products, the additional treatment of those consequences would only increase costs, causing a negative impact on patients, private insurers, and government healthcare programs.

Independent Review of Required Labeling.

17. Drug labeling is intended to provide an accurate and informative statement of the scientific data and information necessary for the safe and effective use of the product. FDA plays a pivotal role in helping to ensure that required labeling for a drug is accurate and informative. The FDA process for reviewing a drug firm's clinical studies leads to approved product labeling that conveys important information related to the safe and effective use of the product for its intended use, such as indications, dosage, precautions, warnings, and contraindications, as well as information regarding the level of efficacy for each approved intended use. Accurate and informative labeling is an essential tool to help ensure appropriate prescribing practices and use of the product; indeed, a product is misbranded if it lacks labeling that adequately informs patients and practitioners how to use the product safely for the uses for which it is intended. An ad hoc communication by a firm about an unapproved use is unlikely to include all of the important information in FDA-approved product labeling. Thus, when medical products are used for unapproved uses, prescribers and consumers do not have the benefit of any FDA-approved labeling related to that use and designed to assure there is adequate information to support safe and effective selection and administration for that use. In the absence of accurate information on how to use a medical product safely and effectively for an unapproved use,

including the lack of such important information as appropriate dosing and contraindications, there is a significant potential for harm to patients.

Independent Review of Marketing Practices.

18. FDA also monitors the marketing of approved drugs to determine whether drugs continue to comply with applicable requirements. This review may include determining whether firms are marketing the product for an unapproved use without complying with applicable premarket review requirements. In establishing FDA's governing authorities, Congress was concerned that firms may manipulate the presentation of information to healthcare professionals in a way that distorts the true safety and efficacy profile to encourage greater use of the product, including for unapproved uses. Presentations that emphasize certain positive data of efficacy, while minimizing or ignoring adverse data (or the absence of sufficient data) regarding safety, may inappropriately influence a healthcare provider's prescribing decisions in a manner that is not in the patient's best interest. Consumers are likewise susceptible to influence by similar marketing practices and consequently may, for example, fail to understand that an adverse event they experienced could be connected to a prescribed drug, and thus fail to follow up with their healthcare providers. FDA's monitoring of marketing practices helps curb the potential for healthcare professionals and consumers to be misled regarding the appropriate use of medical products.

Protection of Human Subjects Receiving Experimental Treatments, Requirements for Informed Consent, and Preservation of the Clinical Trial Process.

19. Congress has further required that investigational uses of drugs be studied in human subjects only if they have given informed consent, and that studies be conducted in accordance with other FDA regulations for the conduct of clinical trials. These requirements are designed

to provide protections to human subjects that may not otherwise be provided when drugs are prescribed to individual patients for unapproved uses. Firms' actions to encourage widespread use of approved drugs for unapproved uses, including by disseminating preliminary scientific information, may also undermine the clinical trial process. Particularly if there is the prospect that they may be assigned to a placebo arm, potential participants who may believe that the product works for their condition may decide not to join a clinical trial designed to rigorously examine safety and effectiveness and to develop data to support the application for approval. This development would impede the collection of data of an adequate quality and quantity to permit a review of the safety and effectiveness of the medical product.

Other Considerations that Inform FDA's Regulatory Enforcement Approach

20. FDA's approach to regulatory enforcement also takes into account other public health interests that, under the appropriate circumstances, may be advanced by the dissemination of scientific or medical information regarding unapproved uses. These public health interests include:

Supporting Informed Decision-Making for Individual Patient Treatment

21. In its premarket reviews, FDA evaluates, among other things, safety and efficacy data gathered and/or generated by the firm to verify whether there are adequate tests to show safety and substantial evidence of efficacy. FDA evaluates this information and makes an approval decision based on a determination of the safe and effective use of the product in the population(s) included in the studies submitted in the application. In making treatment decisions for individual patients, medical professionals may consider whether that patient has characteristics and needs that result in a different risk/benefit calculus as compared to the

characteristics of the study population, and may decide to prescribe an approved product for the treatment of a condition for which it has not been approved. Such practices may be particularly appropriate, for example, in treating patients with diseases for which there is no proven treatment, or in treating a patient who has exhausted all approved treatments.

Furthering Scientific Understanding and Research

22. FDA recognizes the value of sharing reliable scientific information for the purposes of furthering research, such as through hypothesis generation, and increasing scientific understanding in new and developing areas. Sharing information may also allow for collaborative efforts to develop new treatments. Of course, other avenues for sharing scientific developments already exist, such as publishing reports of scientific studies in peer-reviewed journals.

FDA's Tailoring Efforts

23. Under the FDCA, FDA may rely on a manufacturer's communication regarding an unapproved use of an approved drug to help establish that the manufacturer is distributing an unapproved or misbranded new drug, but only where the communication is relevant to the "intended use" of the drug, false, or misleading, and other statutory requirements are met. Whether speech is false, misleading, or relevant and sufficient to infer intended use involves case-by-case examination of the facts. Through guidance documents, FDA clarifies the factors it considers in making these determinations and identifies categories of speech that FDA would not consider to be false, misleading, or, by themselves, evidence of intended use.

24. Central to FDA's implementation of these statutory provisions are their underlying purposes, as described above. FDA recognizes that there can be in certain instances a tension

between the substantial public health interests underlying the premarket review process and other important interests such as furthering scientific research and supporting healthcare provider and patient decision-making for individual patient treatment. Rather than adopt an approach that favors one set of interests at expense of other interests, FDA takes into account all of the varied interests, including First Amendment interests.

25. FDA has issued guidance documents to describe some of the circumstances when it would not consider a manufacturer's distribution of reprints, clinical practice guidelines, or reference texts regarding unapproved uses of approved drugs to be evidence of intended use and/or false or misleading. FDA, Revised Draft Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (Feb. 2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf ("Revised Good Reprint Practices Draft Guidance"); FDA, Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009), http://www.fda.gov/oc/op/goodreprint.html ("Good Reprint Practices Guidance").

26. In addition to the guidance documents on reprints, FDA has issued: Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices – Draft Guidance 6 (Dec. 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf ("Unsolicited Requests Guidance"). This draft guidance states that "FDA has long taken the position that firms can respond to unsolicited requests for information about FDA-

regulated medical products by providing truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved or uncleared indications or conditions of use. If responses to unsolicited requests fall within these parameters, FDA has not expected those responses to meet regulatory requirements for promotional labeling or advertising and has not considered these responses as evidence of intended use." Unsolicited Requests Guidance at 6.

27. These guidance documents describe two sets of circumstances in which FDA would not, under defined circumstances, consider manufacturer communications about unapproved uses of their approved products to be evidence of intended use. However, these guidance documents do not describe the *only* circumstances in which FDA would not take enforcement action with respect to manufacturer communications regarding unapproved uses of approved products. For example, it has long been FDA policy not to object to firms presenting truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences when done so in non-promotional settings and not accompanied by promotional materials. FDA has also stated that it would not ordinarily regard a manufacturer as intending an off-label use for an approved product based solely on the manufacturer's knowledge that an approved product was being prescribed by doctors for such use.

28. FDA is currently engaged in a broad review of its regulations and guidance documents regarding manufacturers' dissemination of information regarding their medical products, and new guidance will be forthcoming to describe its policies more comprehensively.

Application of this Framework to Amarin's Proposed Speech about Vascepa

29. FDA is available to consult with and give its views to manufacturers regarding the possible application of FDA regulations and policies to issues of concern to the manufacturer, including limitations on the promotion of unapproved uses of drugs that have been approved for at least one use. Amarin did not communicate with FDA about the concerns its Complaint describes before Amarin filed this lawsuit. This lawsuit also was filed before FDA had the opportunity to issue new guidance relevant to the type of communications proposed by Amarin in its Complaint. FDA nevertheless considered the issues Amarin has now raised, and issued a letter to Amarin on June 5, 2015, to clarify how its existing guidance and current thinking applies to these proposed communications. A true and complete copy of this letter was previously docketed in this action as Dkt. No. 24. In that letter, FDA recognized the potential value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses, on the one hand, but, on the other, explained in particular that the dissemination of information with a low level of scientific weight, or without the necessary context, could undermine the important public health interests underlying the premarket approval standard for drugs. FDA also noted the unusual combination of circumstances presented, including, but not limited to, the design and results of the ANCHOR trial, the rescission of the ANCHOR SPA agreement based on the developing science, the safety profile of Vascepa, and Amarin's commitment to complete the REDUCE-IT trial. FDA provided Amarin with specific recommendations regarding its proposed communications, based on the circumstances presented by this case.

30. More specifically, in that letter, FDA explained that, in fact, it "would not consider the dissemination of most of [Amarin's proposed] information to be false or misleading, and we do not intend to rely on it as evidence that Vascepa is intended for a use that would render Vascepa an unapproved new drug or misbranded." FDA further explained that it would not object to Amarin's distribution of truthful summaries of the ANCHOR studies and reprints, under the circumstances described in the June 5 letter (many proposed by Amarin), which were designed to help prevent the communication from becoming misleading. FDA therefore would not initiate enforcement action based on such distribution. However, FDA did not condone Amarin's use of a health claim about omega-3 fatty acids and reduced risk of coronary heart disease (permitted for certain dietary supplements and conventional foods through the exercise of FDA's enforcement discretion) in connection with a prescription drug product. Because prescription drugs are subject to a different regulatory regime than foods and dietary supplements, and because of the "low level of scientific evidence" required to support qualified health claims for dietary supplements, dissemination of these claims for a prescription drug could "undermine the important public health interests served by the premarket approval requirements for drugs under the FDCA." The letter continued to advise Amarin that if Amarin were to repackage and re-label its product as a dietary supplement and ensure that the other enforcement discretion criteria for making these claims on dietary supplements were met, "FDA would not object to your inclusion on that dietary supplement of the qualified health claim." FDA therefore would not initiate enforcement action based on that claim in that context. In addition, if FDA were to initiate enforcement action based on any of Amarin's proposed speech, it would not base the action on 21 C.F.R. § 202.1(l)(2) or 21 C.F.R. § 202.1(e)(4)(i)(a) because

FDA does not generally rely on either of these regulations as the basis for its authority regarding manufacturer communications related to unapproved uses of their approved prescription drugs. *See* Revised Good Reprint Practices Draft Guidance, § II.

31. FDA's approach of harmonizing the different interests is tailored to furthering the multiple government interests at stake. With respect to Vascepa, the dissemination of the speech FDA described as potentially objectionable in the June 5 letter would undermine the public health interests advanced by the premarket approval requirements and relevant misbranding provisions described above. A qualified health claim on conventional foods and dietary supplements is, by definition, not supported by the level of scientific substantiation that the FDCA requires for authorized health claims on conventional foods and dietary supplements (significant scientific agreement), nor is it supported by a level of scientific substantiation that is appropriate for drugs. Scientific evidence can reflect different levels of rigor in methodology and evidentiary weight. For purposes of drug approval, effectiveness must be shown by "substantial evidence," often referred to as the "gold standard." "Substantial evidence" is a rigorous standard that requires well-controlled scientific data from adequate and well-controlled clinical investigations. FDA regulations also describe characteristics developed over time that are "recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation." *See* 21 C.F.R. § 314.126(a). These requirements include "a clear statement of the objectives of the investigation" and the "methods of analysis," a study design "that permits a valid comparison with a control to provide a quantitative assessment of the drug effect," measures to appropriately select subjects and minimize bias, and a careful and thorough assessment and analysis of the results. *See* 21 C.F.R. § 314.126(b).

32. FDA recognizes, however, that scientific information regarding studies that do not reach the standard of substantial evidence may still be informative and, potentially, helpful to health care practitioners where the studies are methodologically rigorous and carry sufficient evidentiary weight. For example, FDA has explained that it would not object to the non-misleading dissemination of a manufacturer-distributed reprint where the study in question addressed adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device. These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis.

33. I understand, however, that qualified health claims for dietary supplements and foods are required to be supported with only "credible evidence." Credible evidence may be derived from studies that are not rigorous enough to meet the substantial evidence standard for drugs or the standard described in the previous paragraph for reprints regarding unapproved uses of approved medical products. Furthermore, unlike with effectiveness claims on drug labeling, qualified health claims for dietary supplements and foods can be made under some circumstances even when the weight of the scientific evidence is against the claim, provided there is some credible evidence supporting it. For example, with respect to the subject matter of this lawsuit, I understand that as far back as 1993, FDA found that there is not significant scientific agreement as to the validity of the relationship between omega-3 fatty acids and reduced risk of coronary heart disease. I understand further that, after the decision in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), the agency reconsidered the issue and concluded that

there was still no significant scientific agreement that omega-3 fatty acids reduce the risk of coronary heart disease, but there were "less persuasive" observational studies in which an association (not necessarily a causal relationship) between omega-3 fatty acids and lower risk of coronary heart disease was observed. FDA explained that due to their limitations as observational studies, the "less persuasive" studies provide only supportive rather than direct evidence of such a relationship. Because this credible evidence standard does not provide the appropriate levels of scientific rigor and evidentiary weight that are necessary to provide helpful information regarding drugs to healthcare practitioners, the use of this claim in communications to healthcare professionals about Vascepa, as proposed by Amarin, would undermine the premarket drug approval system and the substantial public health interests advanced by that system.

34. If Amarin were permitted to make effectiveness claims supported only by credible evidence, such as the heart disease claim on dietary supplement labels, in conjunction with its continuing distribution of Vascepa, the incentives to conduct the REDUCE-IT trial would be significantly reduced. Although I understand that Amarin has stated that it intends to complete the REDUCE-IT trial, it is conceivable that Amarin might choose to forego the trial should it prevail in this lawsuit. Were that to happen, the medical and scientific community would be deprived of the robust scientific data promised by the REDUCE-IT trial regarding the safety and efficacy of Vascepa for the use related to cardiovascular disease.

35. In addition, if Amarin decided to abandon the REDUCE-IT trial, it would continue to lack the data necessary for a supplemental new drug application ("sNDA") submission to FDA to seek approval of Vascepa to reduce the risk of cardiovascular disease in statin-treated

patients. Without an sNDA submission, there will be no independent and rigorous premarket review by FDA of the data and information related to the effects of Vascepa on the risk of cardiovascular disease. Consequently, physicians will continue to make prescription decisions without having the benefit of FDA's robust review. Patients who either have or are at risk of having cardiovascular disease would thus be prescribed Vascepa without FDA's assurance that such treatment is effective to reduce the risk of cardiovascular disease.

36. Furthermore, without an sNDA submission containing clinical studies like the REDUCE-IT trial, FDA cannot ensure that labeling will be developed to provide accurate prescribing information for the use of Vascepa in reducing the risk of cardiovascular disease. FDA-approved drug labeling is intended to provide an accurate and informative statement of the scientific data and information necessary for the safe and effective use of that product—and can achieve this only for uses it discusses. Absent an sNDA that contains information sufficient both to support approval for a given use and to inform the development of the related approved labeling, each individual physician is left with the burden of independently trying to evaluate the universe of available data—in its highly variable quality—to determine not just whether to use the drug, but how specifically to administer and monitor it. Undercutting the regulatory structure that incentivizes creation of approved labeling would perpetuate the lack of adequate information to support safe and effective selection and administration of Vascepa for uses that are not yet approved.

37. Amarin's presentation of the heart disease claim in conjunction with its dissemination of the ANCHOR trial summary or reprints about the ANCHOR trial could lead physicians to conclude that the "[s]upportive but not conclusive research" described in the heart

disease claim includes the ANCHOR trial results when, in fact, the ANCHOR trial results do not "show that EPA . . . may reduce the risk of coronary heart disease." The ANCHOR trial results show that EPA reduces triglyceride levels, and based on the totality of the available data, FDA specifically concluded that the reduction of triglyceride levels was not sufficient to show that Vascepa reduces the risk of cardiovascular events in the studied population. Yet, Amarin's use of the heart disease claim together with the ANCHOR trial summary or reprints would suggest that these pieces of information should be considered together, and thus has a potential to mislead physicians into concluding that Vascepa itself will provide a reduction in risk of coronary heart disease by lowering triglyceride levels in patients already on statin therapy who have or at risk for cardiovascular disease. It would be misleading for Amarin to suggest that there is sufficient 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. And allowing Amarin to perpetuate the unsubstantiated claim that Vascepa confers a clinical benefit by lowering triglyceride levels in patients with cardiovascular disease or at risk for cardiovascular disease and on statin therapy would only worsen any misconception about the currently available data and information concerning the relationship between triglyceride-lowering drugs and cardiovascular disease risk. Granting Amarin such license would effectively undo FDA's past and continuing efforts to ensure that physicians have the most accurate and up-to-date scientific information regarding triglyceride-lowering and reducing the risk of cardiovascular events in patients on statin therapy. Even without reference to the ANCHOR trial results, Amarin's presentation of the dietary supplement claim in combination with its distribution of Vascepa could mislead healthcare professionals and cause them to make

ill-informed prescription decisions. For example, on its face, the heart disease claim ("Supportive but not conclusive research shows that EPA and DHA may reduce the risk of coronary heart disease.") does not advise physicians to prescribe EPA as an adjunct to diet or in combination with statins. Physicians could misapprehend this claim, especially if made in isolation, to mean that Vascepa can be prescribed in lieu of diet or statin therapy, which are proven to reduce the risk of cardiovascular events. As a result, patients who are prescribed Vascepa alone may lose the opportunity to select an effective intervention against cardiovascular disease, such as diet or statin therapy.

38. FDA's decisions regarding Amarin's proposed speech described in the June 5 letter were influenced by all of the factors describe above. They reflect a concern that manufacturer communications about unapproved uses are more likely to be helpful to healthcare professionals if they are based on solid science. The recognition that manufacturer dissemination of scientific information about unapproved uses can in some circumstances support certain public health interests is not new; it is inherent in longstanding FDA policies, such as those addressing distribution of reprints of journal articles and unsolicited requests. FDA's policies in this arena are based on the central premise that strong scientific evidence and well-supported conclusions are less likely to result in poor medical decisions than weak or preliminary evidence and unsupported or weakly supported conclusions.

39. FDA's decision not to object to Amarin's distributing the results of the ANCHOR study in the manner described in the June 5 letter was based in part on the nature of the ANCHOR trial and its results, the content of the proposed summary, and the accompanying disclosures. The ANCHOR trial is an adequate and well-controlled trial, and the results of the

ANCHOR trial showed a statistically significant reduction in triglyceride levels over placebo. Disseminating information about adequate and well-controlled trials with statistically significant results is more likely to provide helpful information to healthcare professionals than disseminating information about partially controlled or uncontrolled studies with statistically insignificant results. I also note that the results of the ANCHOR study have been published in the American Journal of Cardiology, *see* Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am. J. Cardiol. 2012; 110:984-992, and publication of study results in this peer-reviewed journal provides additional assurance that the article has been vetted for general adherence to scientific principles and obvious signs of fraud, bias, or omission. In addition, the summary of the ANCHOR results that Amarin provided is factual, contains all the material information, and does not introduce bias. Summaries that possess these attributes, particularly when accompanied with the recommended disclosures, are less likely to mislead than a communication that excerpts, highlights or otherwise alters a publication because these latter types of alterations may omit information and introduce bias.

40. Similarly, peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease that are of the type and distributed in the manner described in FDA's reprints guidances are more likely to be helpful to healthcare professionals than reprints about unsubstantiated studies or opinion pieces with little or no substantive discussion of the relevant investigation or data. The additional disclosures recommended for reprints are intended to help ensure that the communication is not misleading

when distributed in conjunction with Vascepa, which is not the subject of many of reprints in Amarin's list.

41. The heart disease claim is different in kind than the summaries of the ANCHOR trial results and the reprints. The statement—"Supportive but not conclusive research shows that EPA and DHA may reduce the risk of coronary heart disease"—not only characterizes the strength of the research relating to EPA and DHA, but also draws conclusions from that research. In this regard, the claim is more akin to an opinion piece than a reprint about trial results. These types of statements invite healthcare professionals to rely on the conclusions drawn by the manufacturer instead of inviting them to analyze and interpret the data using their own professional judgment. In addition, the express statement that EPA may reduce the risk of coronary heart disease encourages physicians to prescribe Vascepa for that unapproved use in a way that the proposed summary of the ANCHOR results and the reprints do not. Accordingly, use of this claim in connection with the distribution of Vascepa has a greater potential to compromise the integrity of the drug approval regime than the summaries and reprints discussed above.

Proposed Alternatives

42. FDA has examined alternative approaches that have been suggested, for example by the U.S. Court of Appeals for the Second Circuit in *United States v. Caronia*, and determined, based on FDA's technical and policy expertise, that they are impractical, ineffective, unrealistic, or based on inaccurate assumptions. Many of these proposed approaches are blunt tools that may address one or two of the interests identified above, but do not take into account or attempt to navigate the complex mix of numerous and sometimes competing interests that FDA's approach

addresses. The proposed alternatives, and the reasons they would be inadequate substitutes for FDA's current regulatory authorities and enforcement policies in protecting the public health, include the following:

Prohibiting altogether the use and/or prescribing of an unapproved new use of an approved product

43. An outright prohibition on the use of approved products for unapproved uses would be effective in protecting the government interests in motivating scientifically robust research into unapproved uses and ensuring that new uses of an approved drug are proven to be safe and effective before they are used to treat patients. However, this prohibition would substantially restrict the discretion and independence of healthcare providers, and would fail to take into account the interests behind allowing healthcare providers to determine the best treatment options for individual patients in specific circumstances, such as in treating diseases for which there are no approved treatments or in treating individual patients for whom all approved treatments have failed. Thus, this more restrictive alternative would likely have an adverse impact on the public health.

Creating ceilings or caps on the number of prescriptions for an unapproved use

44. This proposed alternative is similar to the total prohibition above, except that it would allow some amount of prescribing before a ceiling or cap was reached. Once the prohibition was operative, it would present the same problem of limiting healthcare provider discretion in determining treatments geared toward the needs of the individual patient. However, before that ceiling was reached, firms could encourage the use of a product for an unapproved use with none of the safeguards of rigorous FDA review—just as if there were no requirement of premarket review for a second intended use. Thus, an arbitrary cut-off of this type is not aligned

to any discernable government interest and would adversely affect the public health. This alternative would also be impractical to administer and enforce because, in many cases, it may be difficult to determine for what specific use a product is being prescribed. Prescriptions written by healthcare providers do not ordinarily reflect whether a drug was prescribed for an approved or unapproved use. With certain limited exceptions (for example, in the case of drugs with significant risks or very high costs where prior authorization is required prior to dispensing), the reason for which a drug was prescribed is not available in the data provided to the Government in claims for reimbursement under Medicare or Medicaid.

Limiting Medicare and Medicaid reimbursement to approved uses

45. This alternative – having the government limit its Medicare and Medicaid reimbursement to approved uses – would again limit healthcare provider discretion in determining treatments geared toward the needs of individual patients under Medicare and Medicaid. There would be no governmental interest in virtually eliminating the prescribing of unapproved uses for one subset of the population but having it continue for the remainder of the population. And, as in the previous alternative, this alternative would be impractical to administer and enforce.

Prohibiting specific unapproved uses that are exceptionally concerning or developing tiers based on level of safety concerns with greater regulatory controls for the relatively more dangerous products.

46. These alternatives would tie the regulatory controls to the degree of safety concerns about the drug. Under the first alternative, the government would prohibit specific unapproved uses for drugs that were exceptionally concerning from a safety perspective. The second alternative would similarly tie the applicable regulatory control to the level of safety concern,

with stronger controls applied to more dangerous products. Both alternatives would be inadequate to protect the public safety because the required safety assessment would depend on the generation of data regarding product dangers before any controls can be applied. It would essentially allow a product to be distributed for unapproved uses without the development of data to support such use and without the submission of the data to FDA, and therefore would allow the product to be in distribution before FDA could assess its safety for that use. It would therefore return drug regulation to the era before the 1962 amendments, when the government was limited to using post-marketing remedies after the product had injured members of the public at large. With respect to the less exceptional or lower tier drugs, both alternatives would undermine the other interest advanced by premarket review by diminishing the incentive to engage in premarket review.

Requiring firms to list all potential indications for a product in the initial premarket application

47. Another proposal is to require manufacturers to list all potential uses in the first application to enable physicians, the government, and patients to track a drug's development. However, science is currently not capable of divining all potential uses of a medical product from an initial study; data and information develop over time through scientific study before and after product approval. If a firm's listing of one or more potential indications, submitted at the same time as the data supporting the primary indication, were the only requirement necessary before firms were allowed to market their product for the claimed indications, this would undermine several government interests listed above, including incentivizing robust research, requiring premarket safety and effectiveness review for each use, and developing appropriate instructions for use. Potential variations on this proposed alternative are likewise unworkable.

For example, if firms were required to obtain approval at one time for all intended uses, the initial application might be significantly delayed while new indications were explored. If a firm were unable to seek approval later for uses that were not identified at the time of an initial application, there would be no incentive to continue scientific exploration that could lead to the development and approval of new medical treatments. Thus, this alternative would negatively impact the public health. For example, Imbruvica (ibrutinib) was approved for Mantle Cell Lymphoma in 2013, then for Chronic Lymphocytic Leukemia in 2014. In 2015, it was approved through the breakthrough therapy designation for Waldenstrom's Macroglobulinemia, a rare form of cancer. It is the only product currently approved for that disease. Similarly, Rapamune (sirolimus) which was initially approved in 1999 as an immunosuppressive agent to help prevent organ rejection. In 2015, it became the first drug to receive approval to treat lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age.

Allowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings

48. This proposed alternative would allow firms to promote an unapproved use limited only by the need to provide certain disclosures. While warnings and disclosures can help to provide material information necessary to assist in understanding data and their value, they are not always effective in curing misleading impressions. Nor do they protect all of the public health interests advanced by premarket review. This alternative would permit firms to bypass the premarket review process for new intended uses once the product was approved for just one use by disclosing that the use is unapproved or including certain warnings. It would therefore undermine the government interests listed above including incentivizing robust research,

requiring premarket safety and effectiveness review for each use, and developing appropriate instructions for use.

49. In addition, a statement that a product is unapproved does not necessarily convey that the speaker does not consider it suitable for that use. Nor do such statements or other warnings substitute for the labeling that is developed after an assessment of the data and information relating to the new use, which labeling would include directions and warnings specifically applicable to that use. Furthermore, studies have shown the limitations of disclosures in terms of consumer perception and understanding in certain contexts—limitations that may exact too great a cost when lives and health hang on their success. Thus, this alternative could return the regulation of medical products to the days before the enactment of current premarket review requirements with only after-the-fact remedies that were insufficient to prevent public health tragedies, and would be detrimental to the public health.

Educating healthcare practitioners and patients to differentiate false and misleading promotion from truthful and non-misleading information

50. Although FDA does have several educational resources in this area, it is unrealistic to suggest that this type of program can be conducted on the scale necessary to effectively combat the adverse impact of false and misleading promotion. But, even assuming that such a program were feasible, this alternative, like the previous proposal immediately above, would allow firms to bypass the premarket review process by marketing or promoting a product for an unapproved use and thereby undermine the substantial government interests in incentivizing robust scientific research, requiring premarket review, and developing required labeling that provides appropriate information for safe and effective use. It would replace the FDA's thorough and rigorous scientific review process with a potentially far more cursory review by

individual prescribing healthcare providers and patients. Individual healthcare providers and patients should not be expected to acquire the tools, background, and specialized expertise in statistics, pharmacokinetics, biomedical engineering, and other fields to conduct a thorough evaluation of the risks and benefits of a new intended use that even roughly approaches that provided by FDA review, and it is unrealistic to suggest that a government-sponsored education campaign would provide this kind of multi-disciplined expertise. And such an education campaign would do nothing to provide each practitioner or patient with the time needed to do so for every use of hundreds of drugs. This suggested alternative also does not appear to take into account the possibility that firms may present truthful but incomplete information, and that the individual healthcare provider or consumer would not be well positioned to uncover or weigh the significance of the absence of a full disclosure of all relevant data.

Reminding healthcare providers of potential malpractice liability

51. This proposed alternative appears to be suggested as a way of making healthcare providers more cautious regarding prescribing medical products for unapproved uses. To the extent it discourages all prescribing of unapproved uses, this alternative would not advance the interests behind allowing healthcare providers to determine the best treatment options for individual patients in specific circumstances, such as in treating diseases for which there are no approved treatments or in treating individual patients for whom all approved treatments have failed. In addition, like the previous example, it would allow firms to bypass the premarket review process for new intended uses and thereby undermine the significant government interests advanced by that process. Furthermore, this alternative would do nothing to deter firms from developing biased presentations with the potential to mislead the listener.

Taxing firms more heavily for sales of products for unapproved uses than for approved uses

52. This proposed alternative would allow unrestricted sharing of information about unapproved uses of approved products, but purports to retain the incentive for seeking FDA approval by taxing sales for unapproved uses more than sales for approved uses. The proposal does not align with the government interests in part because it would affect all prescribing of an unapproved use equally – whether or not there were special circumstances that warranted prescribing for unapproved uses. Moreover, it would allow companies to substitute a tax payment for the cost of the robust scientific research needed to prevent the public from injuries associated with inadequately studied and tested products. It is not apparent how such tax payments would remedy or deter, let alone prevent, the significant public health harms that premarket review is designed to avert. Financially robust entities could, essentially, fund the continued distribution of products with unknown safety and effectiveness profiles while imposing risks on the public. This alternative would also likely be impractical to administer and enforce because it may be difficult to determine in many cases the particular use for which a product is being prescribed.

Executed on June 23, 2015.

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