

EXHIBIT 1

Expert Report of Lawrence Goldkind, M.D.

INTRODUCTION

I have been asked by defense counsel in this matter to render an opinion concerning FDA's position on the labeling of incretin-based drugs with respect to pancreatic cancer.

BACKGROUND

A. Education and Employment Background

I am a medical doctor with specialty training in internal medicine and gastroenterology. I am certified in Internal Medicine and Gastroenterology by the American Board of Internal Medicine, and I have practiced medicine for over 30 years. I received my undergraduate degree from the University of Pennsylvania, *summa cum laude*, and was elected into Phi Beta Kappa. I earned my medical degree at the University of Maryland, where I did my training in internal medicine. I then completed a nutrition research fellowship at Harvard University and a gastroenterology fellowship at Boston University.

I practiced medicine in Tampa, Florida for 11 years before joining the United States Food and Drug Administration (FDA) in 1998 as a Medical Officer in the Division of Gastrointestinal and Coagulation Drug Products in the Center for Drug Evaluation and Research (CDER). After serving as a Medical Officer for two years, I was promoted to the positions of Team Leader (in 2000) and Acting

Division Director of the Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products (DAAODP) (in 2001). From 2001 to 2003, I served as Acting Director of DAAODP. While I was at FDA, I also held a position as a Staff Physician at the National Naval Medical Center (now the Walter Reed National Military Medical Center). I left FDA in 2003 to take up a position as an Assistant Professor of Gastroenterology and Medicine at the Uniformed University of Health Sciences School of Medicine in Bethesda, Maryland, continuing as an attending physician at Walter Reed. After leaving FDA, I also started a consulting practice, consulting with clients on pharmaceutical development and regulatory issues.

I currently teach medical students, internal medicine trainees and gastroenterology trainees. I provide medical care to active-duty military personnel and their families, as well as retired officers and members of the Legislative, Executive, and Judicial branches of the Federal Government. Over the course of my career, I have treated numerous patients with diabetes, pancreatitis, and pancreatic cancer.

A list of materials I have considered in reaching the opinions expressed in this report is attached as Exhibit A. My *curriculum vitae*, which includes a list of publications I have authored, is attached as Exhibit B. A list of cases in which I have testified at trial or at deposition in the past four years is attached as Exhibit C. I am being compensated at my usual hourly rate of \$500.

B. FDA Experience

At FDA, I served extensively as a primary reviewer, as well as supervisory reviewer, of many types of regulatory submissions, including the following: Investigational New Drug (IND) applications; clinical protocols; clinical study reports; adverse event reports; New Drug Applications (NDAs); supplemental NDAs (sNDAs); submissions from sponsors for labeling changes; post-marketing periodic safety update reports; annual reports; and citizens' petitions.

On many occasions, I was also the senior FDA supervisor involved in labeling discussions and industry meetings (including pre-IND meetings, end-of-phase 2 meetings, pre-NDA meetings and post-nonapproval meetings with pharmaceutical sponsors). I have presented on behalf of the Agency at multiple FDA advisory committee meetings, including on labeling issues.

As a Deputy Division Director and Acting Division Director within the Office of New Drugs (OND) at CDER, I had signatory authority for approving drug labels and post-marketing revisions to labeling for approved products. As a Medical Officer and Division Director at FDA, my responsibilities routinely included evaluating safety-related questions based on data analyses performed by FDA staff and/or submitted by sponsors.

OPINIONS

My opinions are based on the materials identified in Exhibit A, and on my education, training, and experience as a physician and gastroenterologist, as well as my FDA experience, including my knowledge of FDA regulations, policies, review procedures, practices, and guidances. I hold the opinions expressed herein to a reasonable degree of scientific and regulatory certainty. I reserve the right to testify in my areas of expertise in response to the opinions of Plaintiffs' experts. I also reserve the right to supplement the opinions included in this report based on new information.

A. FDA's Role in Development, Approval and Labeling of Prescription Drugs

FDA has primary responsibility for regulating prescription drugs in the United States. Both before and after approval, FDA devotes extensive resources and energy to ongoing review of the safety of prescription drugs. FDA typically has in its possession safety data that it has accumulated from the universe of investigational and approved drugs submitted for FDA's consideration—data that are not available to any one sponsor or to the public. FDA may also have data from its own internal studies and analyses.

FDA's review, approval, and oversight process is governed by a comprehensive set of regulations that include very specific guidelines on

appropriate product labeling. FDA considers labeling to be the centerpiece of risk management for prescription drugs. *See generally* 71 Fed. Reg. 3922 (Jan. 24, 2006).

Once a drug is marketed, FDA and the sponsor continue to monitor and investigate the drug's risks and benefits. Specific regulations and guidances govern the continued collection, review, and submission of safety data to FDA. FDA regulations set forth certain information, such as post-marketing adverse event reports, periodic reports, and annual reports, that drug sponsors are required to submit to FDA. If FDA determines that further data are needed to assess a potential safety issue, FDA can request such data from the sponsor and/or require that the sponsor conduct additional studies. FDA can also conduct its own studies as part of its post-marketing oversight of pharmaceuticals.

FDA has a full-time staff that is dedicated to monitoring drug safety. Each division within OND has a deputy division director for safety (with supporting staff) who monitors post-marketing safety within the division that has specific expertise in the disease being treated and knowledge regarding alternative therapies and their associated risks. For example, FDA has reviewed safety information on approximately 50 investigational incretin-based drugs.

In addition, the Office of Surveillance and Epidemiology (OSE) has divisions that deal with the various scientific elements of risk assessment, such as

epidemiology, causality assessment, and risk communication. OSE and the review divisions in OND communicate through the deputy division director for safety within the review division of OND.

FDA has extensive authority to take action concerning a drug and its labeling after it has been approved. FDA may instruct the sponsor to revise its label to add information necessary to inform health care providers fully about the risks and benefits of the medication. Under certain circumstances defined in FDA regulations, sponsors may submit label changes to FDA through a prior approval supplement (PAS) or changes being effected (CBE) supplement. *See* 21 C.F.R. §§ 314.70(b); 314.70(c)(6)(iii). All label changes must be approved by FDA. FDA makes the final determination about the content, placement, and language of the information in the product label in accordance with the regulations. FDA has the authority to make the final determination in order to ensure that the product labeling includes appropriate safety information, but does not include information about risks that are speculative or unsubstantiated. Inclusion of information about risks that are speculative or unsubstantiated may have a negative effect on patient safety—by deterring physicians from prescribing a beneficial medication—and may decrease the usefulness of the product labeling by diluting clinically meaningful information. If a sponsor does not comply with FDA’s instruction, FDA can withdraw its approval of the drug and/or take actions to declare the drug

misbranded and remove the drug from the market. *See* 21 U.S.C. § 331(a); 21 U.S.C. § 334(a); 21 U.S.C. § 352(a); 21 C.F.R. § 314.150 (b) (3).

B. FDA Has Taken an Official Position on the Pancreatic Safety of Incretin-Based Medications and Their Labeling

In March 2013, FDA issued a safety communication in which it announced that it would review data that had raised questions about the pancreatic safety of incretin-based therapies and would communicate its final conclusions and recommendations when its review was complete. In its safety communication, FDA advised health care professionals to continue to follow the prescribing recommendations in the labels for these medications.

In February of 2014, FDA and the European Medical Agency (EMA) co-authored an article in the *New England Journal of Medicine* concerning the safety profile and labeling of incretin-based therapies with respect to pancreatitis and pancreatic cancer. *See* Amy G. Egan, et al., *Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment*, *N. Eng. J. Med.* 794, 795 (Feb. 27, 2014) (the “Assessment”). A month later, FDA issued a response rejecting a Citizen’s Petition, which had asked that one incretin-based product, Victoza, be taken off the market in part because of allegations about a potential connection with pancreatic cancer. *See* FDA’s response to the Citizen’s Petition: Docket No. FDA-2012-P-0404 (March 25, 2014) (FDA’s Citizen Petition Response).

The Assessment and FDA’s Citizen Petition Response each represents FDA’s official position. Per the pertinent FDA staff manual, statements made by FDA staff can be made in connection with “FDA-assigned work” or not. *See* FDA Staff Manual, External Relations: Review of FDA Related Articles and Speeches: SMG 2126.3 (Feb. 2011) (FDA Staff Manual).¹ A publication that is not based on “FDA-assigned work” must contain the following disclaimer: “This [article/speech/presentation/ book chapter] reflects the views of the author and should not be construed to represent FDA’s views or policies.” FDA Staff Manual, § 6.B.11. If a publication is based on “FDA-assigned work,” it may or may not require a disclaimer, at the discretion of the supervisory authority. If FDA-related work does not represent Agency views, it requires a disclaimer. If a publication does not contain the above disclaimer, it represents the Agency’s official position. *See id.* § 6.A. FDA has established a rigorous review and clearance process for FDA-assigned publications. *See id.* I personally published articles while at the FDA. In my experience, FDA adheres strictly to the process outlined in the Staff Manual.

I have reviewed the Assessment, and it is FDA-assigned work and represents the official position of FDA. The article does not contain a disclaimer that the

¹ The manual is available at: <<http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm241089.htm>>.

expressed views may not represent the official views of the Agency. The publication is titled “FDA and EMA Assessment,” and extensively details FDA’s evaluation of a potential association between pancreatic cancer and incretin-based therapies, and explicitly concludes that “FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling” and that “[b]oth agencies agree that assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer . . . are inconsistent with the current data.” Assessment at 796.

FDA’s Citizen’s Petition Response is further evidence of FDA’s careful review of the safety of incretin-based drugs, including the allegations of a possible association between incretin-based therapies and pancreatic cancer. *See* FDA’s Citizen’s Petition Response generally and at 26. This response also represents the official Agency position.

C. FDA Publicized Its Official Conclusions from Its Comprehensive Evaluation of the Scientific Evidence Relating to Pancreatic Cancer and Incretin-Based Therapies.

The Assessment reflects FDA’s robust and comprehensive evaluation of the scientific evidence relating to pancreatic cancer and incretin-based therapies. As the Assessment itself indicates, FDA conducted a “comprehensive evaluation” of a potential safety signal for pancreatic cancer and incretin-based therapies. *See* Assessment at 795.

The breadth and depth of FDA's review was extensive, and included FDA's own independent work on the safety profile of incretin-based drugs. In my opinion, FDA's decision to undertake such an extensive written review for purposes of publishing the results to the public is significant. It evidences FDA's commitment to relaying to prescribing physicians FDA's considered views on the safety profile of these drugs. FDA's review included the following:

- Review of multiple sponsor-submitted and published studies including epidemiologic and post mortem-human studies. FDA even communicated with the authors of a published study, asking them to provide the Agency with more detailed information about the study methodology. It further asked the authors to provide the primary material (histology slides) for detailed review by Agency toxicologists.
- Reanalysis of nonclinical toxicology studies, including having FDA toxicologists review primary materials. This review included over 250 toxicology studies conducted in nearly 18,000 animals. These studies included studies in two species treated for the full life expectancy of the animals at doses well beyond human therapeutic doses.
- FDA issued a post-marketing requirement to the sponsors of three incretin-based therapies approved prior to 2013 using the specific authority of the Food and Drug Administration Amendments Act of 2007 to require animal

studies in various models, including engineered models of diabetes that may magnify, or were thought to magnify, the animals' potential to develop cancer or precancerous lesions. FDA took the extra step of having its own staff pathologists review the primary source material (the histology slides) from one of the studies. In addition, FDA mandated epidemiologic studies be performed by the sponsors of these medications.

- FDA performed its own toxicology studies on both healthy rodents and rodents with chemically-induced pancreatitis in the setting of a diabetic animal model in two species.
- Reanalysis of over 200 clinical trials that involved over 40,000 subjects, of which over 8,000 were exposed for over a year.
- Review of two large, FDA-mandated studies of two DPP-4 inhibitors that included over 20,000 subjects.

Notably, in evaluating the safety of incretin-based therapies, FDA had more information about these products than any one of the drug sponsors. Based on my experience, it is very significant that FDA chose to publish its findings in this manner, and it is also significant that FDA and EMA chose to collaborate to the extent seen here. The fact that FDA took this deliberate step demonstrates the importance FDA attributed to the issue and to ensuring that its findings were clearly communicated to and understood by the public.

FDA concludes the following:

[T]he FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

Assessment at 796.

FDA undertook its Assessment because of assertions “expressed recently in the scientific literature and in the media” concerning a causal relationship between incretin-based therapies and pancreatic cancer. *Id.* Thus, the key question before FDA was whether the labeling should include a reference to pancreatic cancer. FDA’s official conclusion in the Assessment that the labeling was adequate is a rejection of the suggestion that the label should be changed. If FDA had thought that a label change was appropriate, it would have required one at the time of its comprehensive Assessment, if not earlier. FDA reaffirmed its conclusion a month

later when it expressly rejected the Victoza Citizen’s Petition, and again when FDA subsequently approved additional medications in the class without any reference to pancreatic cancer (as discussed below).

The Assessment states that FDA and EMA have not “reached a final conclusion at this time regarding a causal relationship” and “continue to investigate this safety signal.” Assessment at 796. This statement simply reflects that, as a matter of routine practice, FDA continuously monitors every medication for new or evolving information as long as a drug is on the market. Accordingly, the Assessment reflects FDA’s determination that, as of February 2014, the available scientific evidence is neither consistent with, nor supports, a causal association between incretin-based therapies and pancreatic cancer.

D. FDA Has Reiterated Its Position by Rejecting the Victoza Citizen’s Petition and Approving Labeling for New Incretin-Based Drugs that Does Not Warn of Pancreatic Cancer.

In April 2012, Public Citizen filed a Citizen’s Petition to remove Victoza from the market. In the petition, Public Citizen raised a number of potential issues, including pancreatic cancer. In March 2014, after a comprehensive review of the evidence, FDA rejected the Petition in its entirety. On pancreatic cancer, FDA stated that its review, which included evaluation of spontaneous adverse event reports, “found no new evidence regarding the risk of pancreatic cancer . . . that would support any changes to the current approved labeling.” FDA’s Response to

Citizen's Petition at 26. This FDA conclusion reiterates FDA's official position that incretin-based drugs should not be labeled to warn for pancreatic cancer.

Since it rejected the Citizen's Petition, FDA has approved two additional incretin-based therapies, Tanzeum (albiglutide) (April 2014) and Trulicity (dulaglutide) (September 2014). In each case, FDA approved product labeling without any reference to pancreatic cancer. Certainly, FDA would have required that these labels warn about pancreatic cancer if it had believed such a warning was appropriate for incretin-based therapies.

CONCLUSION

Based on my years of experience at FDA and generally in the regulation of pharmaceutical products, it is my opinion (as set forth in more detail above) that FDA's official conclusion in FDA's Assessment and Citizen's Petition Response is that the labeling for incretin-based drugs is adequate and that the data do not support including a reference to pancreatic cancer in the product labels.

I reserve my right to supplement this report.

Executed on December 15, 2014.



Lawrence Goldkind, M.D.