IN THE CIRCUIT COURT OF THE FIRST CIRCUIT

STATE OF HAWAI‘I

STATE OF HAWAI‘I, EX REL. CLARE E. CONNORS, ATTORNEY GENERAL, Plaintiff, vs. BRISTOL-MYERS SQUIBB COMPANY, SANOFI-AVENTIS U.S. LLC, SANOFI US SERVICES INC., formerly known as SANOFI-AVENTIS U.S. INC., SANOFI-SYNTHELABO INC., SANOFI S.A., and DOE DEFENDANTS 2 to 100, Defendants.	)	CIVIL NO. 14-1-0708-03 DEO (Other Non-Vehicle Tort) FINDINGS OF FACT, CONCLUSIONS OF LAW, DECISION AND ORDER Trial Date: October 26, 2020 – November 20, 2020 Trial Judge: Honorable Dean E. Ochiai

INTRODUCTION

This is a civil enforcement action brought on behalf of and in the name of the State of Hawai‘i by its Attorney General ("**State**" or "**Plaintiff**"), against Defendants Bristol-Myers Squibb Company ("**BMS**") and Sanofi Aventis U.S. LLC, Sanofi US Services Inc., formerly known as Sanofi-Aventis U.S. Inc., and Sanofi-Synthelabo Inc. (collectively "**Sanofi**," and, together with BMS, "**Defendants**"), under Chapter 480, Hawai‘i Revised Statutes ("**UDAP**"), Section 661-10, Hawai‘i Revised Statutes, and other applicable Hawai‘i law.[1]

The gravamen of the State's Second Amended Complaint is that Defendants marketed their prescription antiplatelet medication, Plavix (generic name clopidogrel), in an unfair or deceptive manner, in violation of Hawai‘i Revised Statutes ("HRS") Section 480-2 ("HRS § 480-2" or "Section 480-2") and other applicable Hawai‘i law, by failing to warn Plavix patient-consumers and their prescribing physicians that Plavix had diminished or no effect for many patients, particularly those of East Asian and/or Pacific Island ancestry due to the prevalence of genetic variants ("**polymorphisms**") in the enzymes produced in the livers of these patient populations. The State asserts that Defendants engaged in these alleged unfair or deceptive acts or practices from the time that Defendants first began selling Plavix in December 1998 (hereinafter "**launch**") until a "**boxed warning**," also known colloquially as a "**Black Box Warning**," was added to the Plavix label at the insistence of the U.S. Food and Drug Administration ("FDA") sometime in or after March 2010.

In its Second Amended Complaint the State prayed for declaratory and injunctive relief, civil penalties, disgorgement of profits, punitive damages, attorneys' fees, costs of suit, and such other and further relief as the Court deems just in the premises.

By agreement of the parties, this matter was tried before the Court without a jury over a period of four weeks, beginning on Monday, October 26, 2020 and ending on Friday, November 20, 2020. Due to the COVID-19 pandemic the trial was conducted entirely via the Zoom videoconferencing platform.

As set forth in more detail below, the Court finds in favor of the State and against Defendants for the relief set forth herein.

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[1] At one time, the Sanofi Defendants' French parent company, Sanofi S.A., was also a party to this action. However, it was dismissed as a party by agreement on February 14, 2020. [Dkt. No. 726]

Citations to specific evidence herein are merely illustrative and are not intended to reflect the entire body of evidence adduced at trial that supports the Court's findings and conclusions.

FINDINGS OF FACT

1. Plavix, whose generic name is clopidogrel bisulfate (hereinafter "Plavix" or "clopidogrel"), is an oral "antiplatelet" medication in tablet form. "Platelets" are cells that circulate in the bloodstream and bind together – "aggregate" – to form clots when a blood vessel is damaged. Antiplatelet medications are designed to inhibit the aggregation of platelets when the formation of clots is undesirable, for example when a patient has recently suffered a heart attack or stroke and is at risk of another adverse event if the formation of clots is not prevented.

2. Plavix, was developed, manufactured, and placed into the prescription drug marketplace by defendants BRISTOL-MYERS SQUIBB COMPANY, SANOFI-AVENTIS U.S. LLC, SANOFI US SERVICES INC. formerly known as SANOFI-AVENTIS U.S. INC., and SANOFI-SYNTHELABO LLC (hereafter collective identified as "Defendants").

3. In the early 1990's new developments were taking place to treat cardiac events due to narrowing or "clogged" arteries. Balloon catheterization with the installation of an arterial stent was becoming a popular alternative to open heart bypass surgery. This new process was less invasive and produced the desired result without the need for major open-heart surgery.

4. One of the negative outcomes of heart stent insertions was that platelets reacted to the stents and formed clots thereby reducing or stopping the effectiveness of the stent.

5. The formation of clots in the blood vessel of a patient who has recently suffered a heart attack or stroke, or who suffers from other cardiovascular conditions such as peripheral artery disease ("PAD"), can have catastrophic, and often fatal, consequences. The purpose of antiplatelet medications like Plavix is to reduce the risk of such recurrent adverse events by inhibiting platelet aggregation.

6. Plavix is what is known as a "prodrug." Unlike most medications, which are active when ingested, a prodrug must be activated by the patient's body, usually by enzymes in the patient's liver ("hepatic enzymes"), but sometimes by enzymes elsewhere in the patient's

body or other mechanisms of action.[2] If, for any reason, the patient's body fails to bioactivate the prodrug, it is effectively a placebo and remains inert within the body until it is eliminated,[3] in which case the patient receives none of the risk reduction or other benefit intended. If the patient's body only partially activates the prodrug, the patient may, to a greater or lesser degree, receive only partial benefit or risk reduction, which may be insufficient to prevent an adverse event.

7. Plavix is a prescription drug, and like all prescription drugs its marketing, sale and prescription are subject to regulation by the U.S. Food and Drug Administration ("FDA"). The FDA determines the approved uses ("indications") to which a prescription drug may be put, and under what circumstances it may be prescribed. The FDA also issues regulations that impose various obligations on a drug manufacturer regarding labeling of a drug, as well as obligations and limits regarding the manufacturer's marketing of the drug.

8. In order to obtain FDA approval of a new drug, a manufacturer or other "sponsor" must file a "New Drug Application" and subject the drug to a series of preclinical and clinical trials. Preclinical trials involve study of the drug *in vitro* or in animals. Clinical trials involve study of the drug in humans. Clinical trials ordinarily consist of three "phases": (a) Phase I, a study of the drug in a relatively small group of healthy volunteers or patients with the disease/condition over a period of several months in order to determine the appropriate dosage for the drug, how it should be given, and how it affects the body; (b) Phase II, a study of up to several hundred patients with the disease/condition over a period of several months to two years in order to evaluate the drug's efficacy and side effects; and (c) Phase III clinical studies are often referred to as "pivotal" clinical studies because they are the studies upon which the FDA bases its final determination of whether the drug is safe and effective for use in humans for the indication that will be on the drug's label. Phase III studies are large, usually thousands of patients, complex and expensive to perform.

9. The Phase III trial for Plavix (clopidogrel) involved a combined head-to-head comparison of Plavix to aspirin for the treatment of three different cardiovascular conditions,

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[2] An enzyme is a substance, almost always a protein, which acts as a catalyst in living organisms, regulating the speed of biological reactions.

[3] When used herein, terms such as "bioactivate" and "bioactivation" mean the conversion of a prodrug to its active metabolite in order for the prodrug to produce its intended effect.

myocardial infarction (heart attack), ischemic stroke, and peripheral artery disease ("PAD"). The trial is known by the acronym "CAPRIE" (**C**lopidogrel versus **A**spirin in **P**atients at **R**isk of **I**schemic **E**vents).

10. In CAPRIE, Plavix was compared to aspirin because aspirin is also an antiplatelet medication. Aspirin has proven effective (versus placebo) in reducing cardiovascular events in patients with recent heart attack or stroke. In 1997 aspirin was considered the standard of care antiplatelet agent for prevention of arterial thromboses.

11. The results of the CAPRIE study showed only marginal overall benefit over aspirin across the three cardiovascular conditions studied. For patients who enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was numerically inferior to aspirin. The CAPRIE study showed a significant relative risk reduction for study participants with PAD (23.7%), but the risk reduction was less significant for study participants who had suffered a recent stroke (7.3%) and was actually less than aspirin for those who had recently suffered a heart attack (-4.0%). As a result, Plavix was not approved for the primary prevention of heart attack, stroke and/or PAD and was instead approved only for the secondary treatment of patients who had already suffered a heart attack or stroke or who had previously been diagnosed with PAD. This approval was issued on November 17, 1997.

12. When Defendants were seeking approval to conduct the CAPRIE clinical trial they made a commitment to the FDA to study the effects of race during the trial. Yet, when the study was conducted Defendants included only 5% non-Caucasians. Nevertheless, as relevant here, the trial did detect a **statistically significant** disparity in the number of adverse events suffered by non-white racial groups. ("There was a significant interaction between treatment and race (p=0.006), The event rate was higher for clopidogrel in Black patients, Oriental patients, and patients of "Other" race….")

13. This racial disparity in the response to Plavix was contained in Defendants' January 13, 1997 internal report of the CAPRIE study (hereinafter "**CAPRIE Report)**. However, the medical article about the results of that trial, which was published for the broader medical community, made no mention of this statistically significant racial disparity (hereinafter "**CAPRIE Article**"). As a result, outside scientific researchers were denied this important information, which likely impeded the evolution of the science in this area.

14. In February of 1997, the Defendants completed an internal report, "**MIH0012**," which revealed that three Cytochrome P450 genes were principally involved in the metabolism of Plavix within the body, specifically the isoforms CYP2B6, CYP2C19 and CYP3A4, but others – CYP1A2, CYP2C9 and CYP2E1 – might possibly be involved.

15. In March of 1998, prior to Plavix's launch into the commercial market, Defendants completed a meta-analysis of internal data regarding Plavix. (hereinafter "**Meta-Analysis**"). The Meta-Analysis found that almost one-third of Plavix patients (32.2%) had less than 20% response to the drug and 3.4% did not respond to any pharmacological tests used (collectively hereinafter "poor responders").

16. The evidence indicated that this meta-analysis—and its findings that Plavix had a "poor responder" problem—was not shared with the FDA until 2005 (seven full years after the conclusions were known to the Defendants), in an appendix to a separate, subsequent meta-analysis. The State also asserted that, even when the information was eventually disclosed to the FDA, it was "buried" in a large volume of other documents in order to obscure the lengthy delay in its disclosure, as well as its findings.

17. In November of 1998, Defendants completed an internal report, "**MIV0265**," which confirmed the results of **"MIH0012"** that CYP2C19 was one of the enzymes principally involved in the metabolism of Plavix within the body.

18. Defendants launched the sale of Plavix to the public in December 1998.

19. Defendants assert that at the time of launch they did not know precisely how Plavix acted within the body to create its antiplatelet effect, i.e., the inhibition of platelet aggregation. They argue that "science evolves," and therefore their failure to include information that they did not know cannot be unfair or deceptive. However, the State argues persuasively, and several of the Defendants' witnesses conceded that, "science only evolves if you do the research."

20. Further, the evidence presented at trial established that Defendants knew at least the following at the time of launch:

a) Plavix is a prodrug;

b) Plavix is bioactivated by enzymes in the patient's liver;

c) the enzymes necessary to activate a prodrug are often produced by a gene group known as Cytochrome P450 (each one of which is identified by an alphanumeric designation beginning with "CYP");

d) per Defendants' internal reports, CYP2C19 and CYP3A4 were two of the Cytochrome P450 genes principally involved in the metabolism of Plavix within the body.

e) CYP2C19 is and was known to be genetically polymorphic, i.e., had several different variant forms, some of which might potentially be able to activate a prodrug and some of which might not;[4]

f) CYP3A4 is not polymorphic with respect to the activation of Plavix;

g) in other prodrugs known to be bioactivated by CYP2C19, the polymorphisms of CYP2C19 had been shown to be less effective or to have no effect in activating the prodrug;

h) more than four years before the launch of Plavix, CYP2C19 polymorphisms were shown to interfere with the metabolization of drugs, for example in an anticonvulsant named S-mephenytoin, which is a necessary step in the bioactivation of prodrugs metabolized by that gene;

i) the team of researchers who demonstrated the adverse effect of CYP2C19 polymorphisms on the bioactivation of S-mephenytoin (hereinafter "**de Morais Team**") developed a simple PCR-based laboratory test (which was later patented) to identify the CYP2C19 gene and its genetic polymorphisms;

j) in the published article regarding their study, the de Morais Team explained how to conduct their CYP2C19 PCR-based genetic test in a clinical setting, concluding that the PCR-based genetic test for the defective CYP2C19 allele: "will be useful in clinical studies investigating the importance of this genetic defect in drug metabolism in humans." (Exhibit D1098);

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[4] Where a gene has several different variations that are common enough not to be considered mutations, each of the variations is referred to as an "**allele**". Alleles that are unable to activate a prodrug are commonly referred to as **"loss-of-function" alleles**.

k) the CYP2C19 polymorphisms that were shown to have impaired effect on the metabolization of S-mephenytoin (loss-of-function alleles) were known to be significantly more prevalent in East Asians than in other major races by as much as five-fold;

l) every individual has two CYP2C19 genes, one from each parent, both of which may be "normal" or one or both of which may be mutations (abnormalities) or alleles (normal genetic variations);

m) in two additional studies conducted by de Morais, CYP2C19 polymorphisms accounted for 100% of Japanese subjects who were "**poor metabolizers**," i.e., who could not properly bioactivate the prodrug (S-mephenytoin) [P0264] and 100% of Chinese subjects [P0305];

n) there was a group of poor responders to Plavix; and

o) that Plavix patients who are poor metabolizers are likely at higher risk of a recurrent heart attack or stroke than those who are not poor metabolizers.

21. The lack of a uniform patient response to Plavix of the kind that was revealed by the Meta-Analysis has been referred to by a number of names, such as "Variability of Response" ("VOR"), Variability of Platelet Response ("VPR"), "Plavix resistance," "poor metabolism" and "poor response." Given the potential severity of the cardiovascular conditions Plavix was intended to guard against, the discovery that this drug was not working as intended for almost one-third of patients was a matter that would be of great concern to patients and physicians and should have been of great concern to Defendants. Indeed, prior to launch, Defendants' MIH0012 emphasized that it was "important [to] identify[] potential interindividual differences in metabolism and/or clearance due to genetic polymorphism." Defendants further noted that "[t]he use of *in vitro* methods has been recommended to investigate these issues[.]" *Id.*

22. Despite this acknowledgement and Defendants' awareness that: (1) they did not know precisely how Plavix was bioactivated; (2) CYP2C19 played a role in the bioactivation of Plavix; (3) CYP2C19 was genetically polymorphic and its polymorphic nature prevented the activation of other prodrugs; (4) CYP3A4 did not have a known loss-of-function genetic polymorphism that impaired patients' metabolism and pharmacodynamic responses to drugs; (5) Defendants' own Meta-Analysis showed that as many as 32.2% percent of test subjects received less than 20% of Plavix's antiplatelet effect and 3.4% received no benefit at all; (6) the CAPRIE

clinical trial had shown a statistically significant difference in the effectiveness of Plavix for Caucasians versus those of other races; and (7) the various de Morais studies prior to the Plavix launch indicated that CYP2C19 polymorphisms were found to be a 100% predictor of poor metabolizers (for S-mephenytoin), Defendants did not bring this information to the FDA's attention or actively conduct research in an effort to understand the problem and correct it, nor did Defendants try to warn the public or the FDA about these issues. Instead, Defendants, by their words and conduct over the ensuing years, evidenced a clear intent not to conduct or sponsor any research that might confirm the existence of and/or reason for "Plavix resistance" or "Variability of Response" to a patient's race or other identifiable genetic factors.

23. One of the State's medical and regulatory experts, Dr. Laura M. Plunkett presented unrebutted testimony that the Defendants were obligated to update their label to include a warning or precaution about the poor metabolizer issue based on the type of information brought to light by Defendants' 1998 Meta-Analysis, coupled with Defendants' knowledge that CYP2C19 was one of three principal enzymes for the metabolism of Plavix. She also testified that drug companies should be the primary entity investigating potential problems with their own drugs to ensure that their label contains all the warnings and information necessary. Her testimony is supported by the United States Supreme Court, which held:

> [I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. A drug manufacturer is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. Thus, ***when the risks of a particular drug become apparent, the manufacturer has a duty to provide a warning that adequately describe[s] that risk***.

Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1677 (2019) (internal citations and quotations omitted) (emphasis added); *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).

24. Instead of investigating the diminished response to Plavix observed in a significant percentage of the patient population, a limitation known to Defendants at the time of launch, Defendants instituted a policy of systematically opposing any research into Plavix resistance or related issues. Spanning the entire relevant time period, Defendants' internal records repeatedly demonstrated an intent to avoid pursuing the issue. In many instances, their internal statements reflecting an unwillingness to support Plavix-related research were tied to concerns about the potential impact of adverse clinical trial results on sales of the drug.

25. The State's medical experts, Dr. Laura M. Plunkett and Dr. Paul A. Gurbel, testified at trial that at the time of launch, Defendants possessed the means to study the correlation between CYP2C19 polymorphisms and VOR, as well as the correlation between CYP2C19 polymorphisms and clinical outcomes (i.e. heart attacks, strokes, and cardiovascular death).

26. Defendants argued that they did not investigate the impact of CYP2C19 polymorphisms on Plavix Variability of Response because they believed at the time of launch and for many years afterward that the "primary metabolic pathway," i.e., the primary means by which a patient's body produced Plavix's active metabolite, was by way of hepatic enzymes produced by the CYP3A4 gene.

27. In evaluating why Defendants did not discover the cause of the poor response by non-Caucasians reflected in the CAPRIE study and the diminished response for 32% of subjects reflected in Defendants' Meta-Analysis, the Court finds much more persuasive the words and actions reflected in Defendants' corporate records, and testimony consistent with them, which evidence a clear intent by Defendants to avoid any studies that might unearth negative information about Plavix.

28. For example, in **May of 2000**, BMS's medical director proposed supporting a clinical trial to examine the role of race in patients' response to the drug and noted that "such a trial would be small, easy to do, and could be done well in time." (P0603). However, his counterparts at Sanofi quickly admonished him that such a trial "always run[s] the risk to show a difference . . . and then we are really in trouble." Sanofi further warned that such a study "could bear significant risk." *Id.* Shortly, thereafter, Defendants' joint Lifecycle Management Committee ("the LCM"), the internal body responsible for determining which studies and what research to conduct/fund/support, determined "not to be proactive at present" on proposed trials regarding the role of race in Plavix resistance. (P0604). This statement of policy was particularly significant considering Defendants' earlier observation in the CAPRIE Report of "a statistically significant interaction between treatment and race." [5]

[5] At trial, Defendants introduced testimony of current and former executives that the LCM exercised decision-making authority only over "local" studies, which were characterized as small studies to be conducted within a particular country. Defendants asserted that larger, more significant studies were addressed at the "corporate" level. However, Defendants produced no

29. Betraying their own argument, Defendants, in an effort to combat a competitor drug, noted in an internal planning memo that "[a]dditional studies needed; can be small trials to help us to 'shape the debate." (P0430).

30. In **June 2001**, the LCM discussed a proposed study on aspirin resistance, but ultimately rejected it because "it could lead to a similar trial on [Plavix] resistance." (P0607). In **2002**, the LCM continued to reject any studies regarding aspirin because they "could lead to the same questions about [Plavix]," they "could open the door to '[Plavix] non-responders,'" and because there was "no commercial interest" in such studies. (P0608; P0425).

31. Later that year, BMS's medical director acknowledged internally that "Sanofi has generally been 'down' on suggestions to study [aspirin] resistance because they are afraid that '[Plavix] resistance is right around the corner." (P0562). As one of his colleagues noted, "in my opinion, [Sanofi's]/our reluctance to go down the path toward documentation of [Plavix] resistance is understandable, but it will catch up with us and perhaps be an unpleasant and costly surprise when others document it without asking our permission to do so." *Id.* This statement was part of a pattern to conceal, and avoid documenting, facts available to the company but unknown to the public or the scientific community.

32. In **2002**, a study conducted by researchers not affiliated with Defendants was published that reflected resistance to Plavix among 28% of the patient population.[6]

33. In **2003**, several important studies were published. One was conducted by the State's medical/clinical research expert, Dr. Paul A. Gurbel ("Dr. Gurbel"), which found that "[t]here was marked interindividual variability in drug response" in upwards of 31% of the

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persuasive corporate-level documents confirming the otherwise self-serving testimony of its executives that proposals for any large-scale, appropriately powered studies were being considered or approved for the purpose of determining the impact, if any, of a patient's race on their responsiveness to Plavix, and, if such an impact was found, whether genetic polymorphisms were the cause. Significantly, the State's medical/clinical research expert, Paul A. Gurbel, MD, explained persuasively that the larger studies that Defendants did conduct or sponsor were not designed to resolve the VOR issue, or the role of CYP2C19 in the bioactivation process, or the impact of race on variability of response.

[6] Järemo P, Lindahl TL, Fransson SG, Richter A. *Individual variations of platelet inhibition after loading doses of clopidogrel*. J Intern Med. 2002 Sep; 252(3):233-8.

patient population.[7] At the time, Dr. Gurbel was regarded by Defendants as "important and brilliant." For many years thereafter, Defendants considered him "the [world-wide] expert on VPR." (P0583).

34. Subsequent studies published that year confirmed Dr. Gurbel's findings. Nevertheless, Defendants' internal records noted that they "remain[ed] adverse to doing any further research on either aspirin—or [Plavix]—resistance because of the potential negative marketing implications." (P0569). This caused one of BMS's employees to observe that he "had difficulty mobilizing the LCM to address the importance of understanding Plavix resistance through our data and proactive research", and another to note that "[t]here doesn't appear to be a high sense of urgency around this on their [Sanofi's] side." *Id.*

35. In **2004**, Defendants continued rejecting clinical trials whenever "some negative conclusions could be drawn" (P0557), despite their own determination that "it is logical, although not definite, that this variability in response has clinical consequence." (P0507).

36. At a November **2005** meeting at the American Heart Association, Defendants' records indicate that one "Key Opinion Leader" stated that Plavix resistance "is a real phenomenon," however "BMS is putting out anything they can to say it doesn't exist."[8] (P0429).

37. In June of **2006**, a study conducted by researchers not affiliated with Defendants supported the hypothesis that there was an association between genetic polymorphisms in patient CYP2C19 liver enzymes and Plavix VOR. Though it was already established that these CYP2C19 polymorphisms were more prevalent among certain Asian populations, Defendants took no action to update Plavix's label to inform prescribing physicians and patients about Plavix resistance.

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[7] Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. *Clopidogrel for Coronary Stenting: Response Variability, Drug Resistance, and the Effect of Pretreatment Platelet Reactivity*. Circulation. 2003;107:2908–2913. This Court considers it significant that Defendants did not disclose their 1998 Meta-Analysis to the FDA until after this Gurbel study was published.

[8] A "Key Opinion Leader" or "KOL" is an expert, typically a physician, with whom the drug companies work. KOLs are individuals that give advice to the company and who will speak on behalf of the company about a specific product.

38. That same month, during a "Breakout Session" of an "Anti-Platelet Therapy Working Group," a group of Key Opinion Leaders told the Defendants that they had their "head in the sand about . . . clinical resistance." (P0082).

39. Throughout this period, Defendants repeatedly tried to position Plavix in the marketplace as superior to aspirin and other antiplatelet medications, particularly with respect to recent heart attacks. Likewise, at trial Defendants tried to argue that there were no available alternatives to Plavix for treatment of recent heart attacks. However, from even before the Plavix launch, and continuing through at least 2007, the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC"), the division within the FDA responsible for evaluating the truthfulness of a drug manufacturer's marketing campaigns repeatedly advised Defendants that they could not state or imply that Plavix was superior to aspirin because the scientific research did not support such a claim. For this reason, the FDA repeatedly told Defendants that such claims were misleading – specifically using the term "misleading". This occurred with respect to both marketing materials that Defendants submitted to the FDA for prior approval and marketing materials the FDA learned were already in circulation through its routine surveillance program. Thus, the FDA repeatedly told Defendants, over at least the first nine years of Plavix's life cycle, that it was misleading to claim Plavix was superior to aspirin.

40. The Court notes this, not because the State is asserting any claims against Defendants for these kinds of promotional materials, but because the Court views them as a reflection of Defendants' unwavering refusal to accept the reality that Plavix, while potentially a very beneficial medication for many patients (which the State has never denied), was not a "silver bullet" or a "wonder drug" that would cure all ills for all patients. Rather, that it was a drug, like any other, that had its limitations. Those limitations could potentially contribute to very significant harm, including death, to large groups of patients unable to bioactivate it, or only able to activate it partially. The Court makes a point of this because that seemingly blind refusal to accept the reality of Plavix's limitations has apparently continued to the present, including the course of this four-week trial.

41. Because Defendants' position is so at odds with the evidence against them – evidence that in many cases consists of their own internal corporate records – it could not help but affect this Court's view of Defendants' candor and credibility. The Court found that many times Defendants told only part of the story.

42. For example, Defendants presented expert testimony that according to the American Heart Association ("AHA") and the American College of Cardiology Foundation ("ACCF") Plavix is the "gold standard" for treatment of cardiovascular conditions, with a "Class 1" recommendation (the highest recommendation available) by the AHA/ACCF. But it was soon brought to light that Plavix has a Class 1 certification only for certain specific conditions and procedures, and only when it is prescribed with aspirin as part of a dual antiplatelet therapy program. One of Defendants' medical experts, Todd Seto, M.D., conceded this point when pressed.

43. In a similar vein, most of the clinical studies Defendants relied on to support their claim that Asian CYP2C19 poor metabolizers do no worse on Plavix than other patients involved dual antiplatelet therapy ("DAPT") in which patients were given not just Plavix but also aspirin. Dr. Seto conceded on cross-examination that he does not know, and does not have an opinion, whether the inhibition of platelet aggregation that a CYP2C19 poor metabolizer experiences while undergoing DAPT is due to the Plavix or to the aspirin. This concession entirely undermined the probative value of the DAPT-based studies and Defendants' suggestion that these studies mean Plavix works just as well for CYP2C19 poor metabolizers.

44. Throughout **2007 and 2008**, further studies indicated that CYP2C19 polymorphisms were responsible for poor patient responsiveness to Plavix. Beginning in late 2008, and continuing throughout **2009**, additional studies established that CYP2C19-based poor responsiveness to Plavix led to an increased risk of cardiac events (i.e. "clinical outcomes") when compared to patients who were normal or intermediate responders.

45. Shortly before these studies regarding clinical outcomes emerged, clinical researchers determined that when Omeprazole (a proton-pump inhibitor) was given to a patient who was also taking Plavix, the Omeprazole interfered with the functioning of the CYP2C19 alleles and caused a corresponding reduction in Plavix's antiplatelet effect. This caused significant concern at the FDA, where key personnel pressed Defendants regarding the clinical implications of that study, the scientific history of VOR, and how the label should be updated to reflect this critical information.

46. While these discussions were underway, a study conducted by researchers not associated with Defendants was published in the New England Journal of Medicine which found that "[a]mong persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele

had significantly lower levels of the active metabolite of clopidogrel, **diminished platelet inhibition**, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers" (emphasis added) (hereinafter "**Mega Study**). The results of this study, in conjunction with the Omeprazole issue, prompted the FDA to insist on addition of language in the Plavix label explaining the CYP2C19 poor metabolizer phenomenon and noting the availability of genetic testing.

47. At trial, there was conflicting evidence regarding Defendants' response to the proposed label change. Defendants presented some evidence suggesting that Defendants worked collaboratively with the FDA to effect the label change. On the other hand, the State presented evidence suggesting that Defendants were more resistant to the label change, with Defendants arguing that the relationship between CYP2C19 polymorphisms and potential outcomes "is not yet fully understood." When the FDA continued to insist on the inclusion of VOR-related information in Plavix's label, Defendants sought help from their stable of "Key Opinion Leaders" ("KOLs") – doctors and scientists Defendants relied on to publicly speak favorably about Plavix – hoping to push back against the FDA's insistence. In an internal email following such an effort, one employee informed his colleagues that their KOLs would provide no such support, stating:

> I have to tell you that I have had in depth 1:l's with about 6 senior KOLs since I have been at [the American College of Cardiology] and the mood is very negative toward us (people like Dr Topol, Gurbel, Eikelboom, Fox are all saying that ***they have been telling us this for years and we chose to ignore them and bury our head in the sand and so they feel no sympathy toward our current situation!***). Therefore, my concern is that we cannot look to KOL support should the FDA follow through.

(P0533) (Emphasis added)

48. In May 2009, the FDA required Defendants to add information to the Plavix label regarding CYP2C19 and poor metabolizers. The following information was also included regarding the many studies that established a link between CYP2C19 and clinical outcomes:

> To date, the impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel's active metabolite has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the CMax and AUC of the active metabolite by 30-50% following 300 and 600mg loading doses and 75mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition

> or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolizers in 21 reported studies involving 4,520 subjects. The relative difference in antiplatelet response between genotype groups varies across studies depending on the method used to evaluate response, but is typically greater than 30%.
>
> The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post-hoc clinical trial analyses (substudies of CLARITY-TIMI 28 [N=465] and TRITON-TIMI 38 [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY-TIMI 28 and one of the cohort studies (n=765; Trenk), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n=3,516; Collet, Sibbing, Giusti), patients with an impaired metabolizer status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In the fifth cohort study (n=2,208; Simon), the increased event rates were observed only in poor metabolizers.
>
> Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

(P0410 at nn. 1-6 and accompanying text) (Footnotes omitted).

49. This information was included in the Pharmacogenetics section of the Plavix label. But very shortly thereafter, in March of 2010, the FDA took the additional step of requiring Defendants to place this information in a "boxed warning," also known as a "black box warning," and to move information regarding this issue to the "Warnings and Precautions" section of the label.

50. A boxed warning is a section of the drug label reserved for serious warnings, particularly those that may lead to death or serious injury.

51. The 2010 boxed warning stated the following:

> **WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE**
>
> **The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do**

patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)].* Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. *[see Dosage and Administration (2.3)].*

(Emphasis in original)

52. In 2016, the boxed warning was modified to state the following:

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)].* Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.5)].* Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

(Emphasis in original)

53. Defendants argued at trial that they could not have included the above information in the Plavix label prior to March of 2010 because they did not "know" of the information prior to late 2008/early 2009. However, the record establishes that at all times relevant hereto, Defendants knew, or should have known, all necessary and relevant information.

54. On July 21, 2020, the Court granted the State's motion for partial summary judgment that the information contained in the 2016 boxed warning was "material" within the meaning of Hawaii's UDAP statute.

55. Defendants argued at trial that the change in the 2016 boxed warning deleted any reference to a causal relationship between CYP2C19 poor metabolizer status and clinical outcomes. But since the boxed warning remains on the Plavix label, Defendants' argument is unpersuasive.

56. The "Medication Guide" portion of the Plavix label, distributed by Defendants themselves, which is directed to consumer-patients—and which patients are instructed to read before they "start taking Plavix and each time [they] get a refill"—stated in both 2016 and today that the information in the boxed warning is "the most important information [you] should know about Plavix."

57. At trial, the State presented the expert testimony of Paul A. Gurbel, MD, a renowned participant in the field of clinical research regarding prescription drugs, and in particular, Plavix.

58. Dr. Gurbel earned his medical degree at the University of Maryland School of Medicine and completed an internship and residency in internal medicine at Duke University Medical Center. He then completed a fellowship in pulmonary and critical care medicine at Johns Hopkins University, followed by fellowships in cardiovascular disease and interventional cardiology, as well as a chief residency in internal medicine at Duke. He is board certified in internal medicine, cardiovascular disease, and interventional cardiology by the American Board of Internal Medicine. In addition to prolific research, Dr. Gurbel remains a practicing clinical cardiologist, cardiac interventionalist, and leading expert on Plavix.

59. Dr. Gurbel serves on the editorial boards for several journals, including *Journal of the American College of Cardiology, The American Heart Journal, Journal of the American College of Cardiology Heart Failure, Circulation, The Journal of the Royal Society of Medicine,* among others. He is also a reviewer for the *New England Journal of Medicine* and has authored over 450 major articles in peer-reviewed journals.

60. Dr. Gurbel's research and concepts have been published in over 1,000 peer-reviewed documents. In 2012 alone, he authored 30 manuscripts in the peer-reviewed literature and, in fact, in that year three peer-reviewed papers developed by Dr. Gurbel and his team were named "most Important Papers in Antiplatelet Therapy" by the prestigious medical journal *Circulation.*

61. Since shortly after Plavix was first introduced to the market, Dr. Gurbel's research has paved the way in understanding its effects. His laboratory pioneered the concept of antiplatelet response variability, a significant limitation of clopidogrel effetiveness. Dominique Roome, a senior medical employee at Sanofi who testified at trial and who was intimately involved with Plavix over the years, readily agreed that she has referred to Dr. Gurbel as an "important and brilliant" Key Opinion Leader, and the world-wide specialist in Variability of Response. Defendants' clinical research expert, Sonia de Morais, MD – the same de Morais who identified the CYP2C19 polymorphisms and their relationship to Variability of Response and race in the mid-1990s, and who developed and later patented the genetic test to identify the various CYP2C19 polymorphisms – likewise expressed deep respect for Dr. Gurbel.

62. At trial, Dr. Gurbel explained why he focused so much of his research on Plavix, stating, "[Y]ou have to remember that, that thrombosis in the coronary artery is what kills the patient, the No. 1 cause, that's why people die. They develop a clot … they may not survive and have ventricular fibrillation and die. But the No. 1 event, the primary event that closes the artery is aggregation of platelets. So this drug particularly, what we're talking about today, has to be relied on to work all the time. It's not like a statin, it's not like a blood pressure pill, it not like an analgesic. This is the drug given to the patient to prevent the catastrophe. … Doctors … were relying on this workhorse drug to prevent the fatal event. So I felt that it was really important, particularly with this drug, to understand the limitations of the drug, and that everyone involved in the care of the patients, and the patients themselves, being informed consumers and understanding whether to get a stent or whether they get bypass surgery to treat their problems, to know whether they can truly rely on this drug to work all the time." Transcript ("Tr."), 11/2/20 A.M., at 53:25-55:7.

63. Dr. Gurbel testified that he first expressed concern to Defendants about the lack of platelet inhibition in some patients in approximately 2001.

64. Responding to Defendants' assertion that they conducted many studies into Variability of Response, Dr. Gurbel testified: "They didn't. … I would say broadly, you know, any meaningful research, no." Tr. 11/2/20 A.M., 93:8-17. "I would submit to you that I'm aware of all the meaningful research in this sphere that's ever been done, and there has been, as far as I know, being an expert in this area, publishing over 200 manuscripts on clopidogrel and its antiplatelet effect, that there has been no meaningful research that I know of by the defendants to address this issue of variability of response and its clinical importance." *Id.* at 78:4-11.

65. Responding to defense arguments that a study of 45,000 Chinese in a clinical trial known by the acronym "COMMIT" demonstrated that Plavix works just as well for East Asians as for other races, Dr. Gurbel testified: "What I'm trying to teach you about this, is that the COMMIT study had a relative risk reduction, you see, it's 9 percent, sir. The CURE study [made up primarily of Caucasian patients] had a relative risk reduction of 20 percent. That means that clopidogrel was half as effective clinically in the COMMIT study than in the CURE study. COMMIT had 100 percent Chinese. It was a hugely powered study, 45,000 patients it took to show that meager 9 percent risk reduction. That's the size of a study you need to have to show efficacy, as small as 9 percent. So, there is no question that the COMMIT study

demonstrated totally clearly that there's less efficacy in Chinese from clopidogrel, as compared to CURE, which is Caucasian. That is the clearest evidence of a reduction in treatment efficacy that can be shown up to 2020 between the races. Tr. 11/5/20 at 135:6-23.

66. Responding to Defendants' contention that they could not conduct studies that would establish a link between CYP2C19 poor metabolizers and Variability of Response because the technology was not available to identify the active metabolite, Dr. Gurbel testified:

> Q. And what technological limitations were there, if any, in 1997 or 1998 that would have prevented such a study from being undertaken?
>
> A. Well, the mutation in – in 2C19 that caused the dead gene was identified in landmark work by de Morais published in the Journal of Biological Chemistry [in the early and mid '90s], a very prestigious journal. And so there was an assay that she developed that could have been used.

Tr. 11/2/20 PM, at 66:18-25.

> A. … You're asking me what could have been done. I mean, there was an assay that was available that was – her lab developed that was being used – they identified the cause of this ethnicity-based poor metabolizer – poor metabolism. Any you could – those patients could have been genotyped and given the drug and their antiplatelet effect could have been examined.
>
> Q. So were there in fact any sort of technological scientific limitations that would have prevented that kind of study from taking place in 1997?
>
> A. No. I mean, they had the – de Morais had the PCR, the assay. I don't – I don't see why it couldn't have been done. If there's an assay available and you know how to measure platelet function, you can do the study. I mean, that's what we did in our studies. We determined the genotype in patients undergoing stenting and we gave them clopidogrel. … [T]hat's totally a doable study.

Id. at 67:1-18.

67. Dr. Gurbel also explained why he and his colleagues were only able to conduct smaller studies when Defendants refused to fund them or supply the drugs needed for larger studies: "We needed funding. So it's a simple matter of funding. … [T]here's no lack of interest from these investigators around the world. But to put together a large-scale trial, such as a study in the tens of thousands, like has been done to get 15,000 to get the approval of clopidogrel in the CAPRIE trial, or 45,000 in a Chinese population with myocardial infarction, STEMI[.] …

[U]sually the funding comes from private industry, or it comes from a device manufacturer. The only caveat there is that private industry is not going to want to niche their drug. … [T]hat cuts into market share, and total sale of the drug. … So without big pharmaceutical interest to fund it, I don't see how these studies ever get done." Tr. 11/5/20 at 33:1-34:9.

68. The State also offered the testimony of pharmacology, toxicology and prescription drug regulation expert Laura M. Plunkett, DABT, at trial.

69. Dr. Plunkett is a pharmacologist, toxicologist, and a United States Food and Drug Administration ("FDA") regulatory specialist. She is board-certified as a Diplomate of the American Board of Toxicology and has authored or co-authored numerous scientific publications. She received her undergraduate degree from the University of Georgia and a Ph.D. in pharmacology in 1984 from the University of Georgia, College of Pharmacy. Her doctoral research was focused in the area of cardiovascular pharmacology, which is the study of mechanisms underlying drugs used to treat diseases or conditions of the cardiovascular system

70. Dr. Plunkett has over thirty years of experience in the areas of pharmacology and toxicology and has worked in both government and academic research. She has taught pharmacology and toxicology at the undergraduate and post-graduate levels. As a pharmacologist, much of Dr. Plunkett's consulting work has related to understanding and explaining the mechanisms of action of drugs of all types, as well as the toxic effects of drugs. She has a specific expertise in cardiovascular pharmacology, which is the study of drugs used to treat cardiovascular diseases, including antithrombotic drugs. She also has an expertise in pharmacokinetics, which is a discipline within the general area of pharmacology that relates to the way drugs are absorbed, distributed, metabolized and excreted from the human body. Dr. Plunkett has designed clinical trials and analyzed pharmacokinetic data.

71. As a result of her training and work with various clients, Dr. Plunkett has knowledge, experience and expertise related to changes in the FDA regulations over the years from the initial passage of the Federal Food Drug and Cosmetic Act in 1938 up to the most current amendments to the FFDCA. She has published dozens of peer-reviewed articles. She has also authored a book chapter on FDA pharmacovigilance practices and served as a peer-reviewer for medical journals in her capacity as a pharmacologist and toxicologist. She has provided expert testimony and been qualified by both state and federal courts in the areas of pharmacology, pharmacokinetics, toxicology, risk assessment and FDA regulations.

72. Dr. Plunkett testified, among other things, that, in practice, under the criteria set forth in the applicable FDA regulations Defendants would have been obligated to update their label to include a warning or precaution about the poor metabolizer issue based on the type of information brought to light by Defendants' 1997 Meta-Analysis, coupled with Defendants' knowledge that CYP2C19 was one of three principal enzymes for the metabolism of Plavix. Tr. 10/27/20 A.M. at 71:5-72:2.

73. Dr. Plunkett also testified that, in practice, under applicable FDA regulations Defendants were permitted to add or strengthen a warning or precaution about the poor metabolizer issue without first seeking approval from the FDA.

74. Addressing Defendants' contention that they had no duty to investigate the reasons for the diminished response to Plavix reflected in the Meta-Analysis and other available information, Dr. Plunkett testified that drug companies like Defendants "absolutely" have an obligation to investigate potential problems with their drugs, stating: "That's the basis for why pharmacovigilance and post-market surveillance or continual analysis of data goes on once the drug [is] approved. The paradigm for drug development and approval is that when you are developing a drug, it is understood that you're testing it in a – in a more selective population for the purposes of the clinical study that may or may not be relevant to the real-world experience of patients. So as a result they're – under Section 21 CFR 314, there are specific requirements for companies to perform this type of surveillance of their drugs and the literature, as I talked about earlier, in order to understand whether or not there are risks out there that are different either in terms of something you hadn't seen in your clinical development or you may be seeing it at a greater frequency than you had seen it in your initial clinical development. Or you may be seeing it like in this case where the benefit was shown in the clinical trial, but when it gets out in the real world, there are people that may not appear to be getting the benefit of the real drug. So those are the kinds of things that are a part of good pharmacovigilance practice." Tr. 10/26/20 at 126:16-127:17.

75. Like Dr. Gurbel, Dr. Plunkett testified about the importance of drug companies to fund clinical trials, stating: "The reason is that the company who makes the drug is going to have the resources to provide the drug to the investigators and also the source of knowledge. It's the single best source of knowledge about the drug itself. As a result, it's difficult sometimes to get funding for large clinical studies that are – can be expensive from sources outside in private

grants and things like that. So it is actually important that companies are willing to work with outside investigators to get studies done that involve their drugs." Tr. 10/27/20 P.M. at 92:9-20.

76. Regarding the Defendants' claim that they have conducted numerous studies relating to the poor metabolizer issue, Dr. Plunket testified: "I haven't seen a large clinical trial that has been done by the company or anyone else of the power to be able to answer definitively those questions, and specifically for the individuals that carry two loss-of-function alleles, we haven't completely defined that. No study has been done. But we do know there's an increased risk." Tr. 10/27/20 P.M. at 46:21-47:6.

77. Defendants' trial witness list identified an expert to respond to the opinions of Dr. Plunkett, but when it came time for her to be called to testify Defendants elected not to call her. Therefore, Dr. Plunkett's opinions were unrebutted at trial.

78. Having weighed the admissible evidence presented at trial, and having taken into account the credibility of the witnesses and other evidence presented, the Court finds that Defendants knew at the time of launch that there was a significant issue regarding diminished patient response to Plavix, particularly in those of non-Caucasian races; that for many years Defendants deliberately turned a blind eye toward the problem out of concern that addressing it might adversely affect Plavix sales and Defendants' profits; that Defendants deliberately withheld vital information from the FDA and the greater medical community about the issue; that Defendants engaged in a pattern and practice of rejecting any proposed studies that might call attention to or generate interest in the issue of Plavix Variability of Response; that Defendants failed to conduct any studies that were designed and adequately powered to investigate Plavix Variability of Response and/or the impact of race and/or CYP2C19 polymorphisms on inhibition of platelet response in Plavix patients; that by engaging in the foregoing conduct Defendants intentionally set back the progress of research into the Plavix Variability of Response issue by many years; and that by doing so Defendants knowingly placed Plavix patients at grave risk of serious injury or death in order to substantially increase their profits.

79. For these reasons, the Court finds that the Defendants were engaged in unfair and deceptive practices in Hawai‘i regarding Plavix since its launch in December 1998, and that such violations continued until the boxed warning was added to the Plavix label sometime in or after March 2010.

80. At trial, the State presented expert testimony from Nicole Maestas, Ph.D., regarding the number of retail prescriptions, refills and non-retail units sold in Hawai‘i between December 1998 and March 12, 2010. Dr. Maestas is an associate professor of Health Care Policy at Harvard Medical School and a research associate at the National Bureau of Economic Research. She is an economist with broad training in the fields of health economics and health policy whose research concerns the economics of health care utilization, health insurance, and health outcomes. She has many years of experience analyzing health care data of different types, including prescription drug claims, using a wide range of methodologies.

81. Dr. Maestas calculated the number of retail prescriptions, refills and non-retail units sold during the relevant time period to be 834,012.

82. The Court found Dr. Maestas's testimony to be both helpful and credible, and Defendants offered no expert testimony or even argument to dispute or otherwise counter her calculations. Therefore, the Court finds that 834,012 Plavix retail prescriptions, refills and non-retail units were sold in Hawai‘i between December 1998 and March 12, 2010.

83. If any of the Findings of Fact set forth herein shall be deemed Conclusions of Law, they are hereby incorporated by reference in the Conclusions of Law set forth below.

CONCLUSIONS OF LAW

84. The Court has jurisdiction over the parties and the claims in this case.

85. The Attorney General is authorized to bring this action in the name of the State of Hawai‘i under Hawai‘i Revised Statutes ("HRS") Chapter 480 ("UDAP") and under HRS § 661-10.

86. HRS § 661-10, grants the Attorney General broad authority to bring claims in the name of the State "[w]henever it is necessary or desirable … in order to collect or recover any money or penalty … or enforce any other right[.]" HRS § 480-3.1 grants the Attorney General the authority to bring a civil action for civil penalties against "[a]ny person, firm, company, association, or corporation violating any provisions of section 480-2[.]"

I. THE STATE'S UDAP CLAIMS

87. HRS § 480-2 declares unlawful any "unfair or deceptive acts or practices in the conduct of any trade or commerce[.]"

88. Hawaii's UDAP statute "outlaws unfair methods of competition and unfair or deceptive trade practices in **sweeping terms.**" *Han v. Yang*, 84 Hawai'i 162, 177, 931 P.2d 604, 619 (App. 1997) (Emphasis added). The statute "was constructed in broad language in order to constitute a flexible tool to stop fraudulent, unfair or deceptive practices for the protection of both consumers and honest businessmen [and businesswomen]." *Id.* To state a claim under UDAP, the State need only prove that Defendants engaged in "[u]nfair or deceptive acts or practices in the conduct of any trade or commerce." HRS § 480-2(a). "To violate HRS § 480-2, a practice need only be unfair or deceptive, not both." *Bald v. Wells Fargo Bank, N.A.*, 688 Fed.Appx. 472, 475 (9th Cir. 2017).

A. Deceptive Acts or Practices of Defendants

89. A deceptive act or practice is defined as having "the capacity or tendency to mislead or deceive." *Courbat v. Dahana Ranch, Inc.*, 111 Hawai'i 254, 261, 141 P.3d at 434 (2006). To establish a deceptive act or practice under § 480-2, the State must show "(1) a representation, omission, or practice that (2) is likely to mislead consumers acting reasonably under the circumstances where (3) the representation, omission, or practice is material." *Courbat,* at 262, 141 P.3d at 435.

90. The test for deceptiveness is "an objective one, turning on whether the act or omission 'is likely to mislead consumers,' as to information 'important to consumers,' in making a decision regarding the product or service." *Id.* (internal citations omitted). The State must therefore prove by the "objective 'reasonable person' standard" that the representation or omission was deceptive. *Id.* at 263, 141 P.3d at 436. A UDAP violation need not involve a representation; it can involve other acts or practices. *Yokoyama v. Midland Nat. Life Ins. Co.*, 594 F.3d 1087, 1092 (9th Cir. 2010) (UDAP violation can involve "a representation, omission or practice").

91. The State "need not establish an intent to deceive on the part of the defendant, nor any actual deceit." *Courbat*, 111 Hawai'i at 262 fn.9, 141 P.3d at 435 (citations omitted). "Proof of actual deception is unnecessary" because the relevant inquiry is whether a representation, omission, or practice has "the capacity or tendency to mislead or deceive." *Tokuhisa v. Cutter Management Co.*, 122 Hawai'i 181, 195, 223 P.3d 246, 260 (App. 2009); *Hungate v. Law Office of David B. Rosen*, 139 Hawai'i 394, 411, 391 P.3d 1, 19 (2017); *State ex rel. Bronster v. U.S. Steel Corp.*, 82 Hawai'i 32, 51, 919 P.2d 294, 313 (1996).

92. As noted in Finding of Fact No. 54 above, the Court has already determined that the information in the 2016 boxed warning was material. Findings of Fact, Conclusions of Law, and Order Granting Plaintiff's Renewed Motion for Partial Summary Judgment Regarding the "Materiality" of Information Contained in the Plavix "Black Box Warning," filed July 21, 2020. [Dkt. No. 1023].

93. Here, the Court finds that the evidence presented shows that Defendants engaged in deceptive acts or practices when they failed to include information equivalent to that in the product label during the time period of December 1998 to March 12, 2010. The Court finds that the evidence before it overwhelmingly supports a conclusion that Defendants' acts and practices during the relevant period led to the omission of information crucial to physicians and patients.

94. The Court acknowledges that the Defendants could not have placed a "Black Box Warning" on the label without the FDA's prior approval. However, Defendants had the ability to update the label, specifically to add or strengthen a warning, under the Changes Being Effected ("CBE") regulations of the FDCA. *See* 21 C.F.R. § 314.70(c)(6)(iii)(A); *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019).

95. Further, the Court finds that Defendants had sufficient knowledge, after FDA approval but prior to launch, to change the Plavix drug label to warn patients and physicians about the lack of response exhibited by certain patients. The Court also finds that Defendants had sufficient knowledge, as well as the technical ability, to investigate the cause of variability of response which was known to Defendants before the drug launched in December of 1998.

96. Defendants argued repeatedly throughout trial that they did not know or could not have known the extent to which CYP2C19 played a role in the metabolism of Plavix or in variability of response to Plavix. Defendants also argued that they could not possibly have determined whether people with CYP2C19 polymorphisms experienced diminished effectiveness from the drug. The Court is not persuaded by the Defendants arguments. The facts presented show that Defendants had sufficient knowledge, technology, and ability to update the Plavix label from launch and continuing for many years. Yet, instead Defendants chose to establish a policy of inaction and denial.

97. The Court finds that the omission of this material information was likely to mislead consumers. The ability to give informed consent during medical treatment is a well-established tenet of our jurisprudence. As testified at trial by another of Defendants' medical

experts, Dr. John Kao, doctors generally inform their patients about all risks and benefits of the drugs they prescribe so that the patient can make an informed decision concerning their course of treatment. Omitting information from a drug label about the efficacy and safety profile of a drug such as Plavix, that is intended to lower the risk of a recurrent heart attack or stroke, certainly has the capacity and likelihood to mislead consumers. The evidence shows that Defendants deliberately hid material information from consumers that could have affected their choice of, or conduct regarding Plavix. Therefore, the Court finds that, based on the evidence presented at trial, all the elements for a claim of deceptive acts or practices have been met.

B. Unfair Acts or Practices of Defendants

98. Under UDAP, a practice "is unfair when it [1] offends established public policy and [2] when the practice is immoral, unethical, oppressive, unscrupulous or [3] substantially injurious to consumers." *Hungate, supra*, 139 Hawai'i at 411, 391 P.3 at 18, quoting *Hawai'i Community Federal Credit Union v. Keka (Keka)*, 94 Hawai'i 213, 228, 11 P.3d. 1, 16 (2000). A UDAP plaintiff need not prove all of these elements. *Id.* Rather, "[a] practice may be unfair because of the degree to which it meets one of the criteria or because to a lesser extent it meets all three[.]" *Id.*, quoting *Kapunakea Partners v. Equilon Enters, LLC*, 679 F.Supp.2d 1203, 1210 (D. Haw. 2009).

99. The Court finds that the conduct of the Defendants in this case also constituted unfair acts or practices under § 480-2.

100. First, the Court finds that Defendants conduct in this case offends established public policy. In order to show that a practice is unfair because it offends established public policy, such policy must have been "established by statutes, the common law, or otherwise." *Hungate, supra*, 139 Hawai'i at 411, 391 P.3 at 18. In cases like this one, the Supreme Court of the United States has repeatedly acknowledged:

> [I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. A drug manufacturer is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. Thus, ***when the risks of a particular drug become apparent, the manufacturer has a duty to provide a warning that adequately describe[s] that risk***.

Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1677 (2019) (internal citations and quotations omitted) (emphasis added); *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).

101. The Court finds that Defendants' failure to update the Plavix drug warning after learning of the safety risks posed to poor metabolizers offends this well-established public policy. Defendants compounded their unfair conduct by suppressing research and continuously and repeatedly failing to further investigate the risks of reduced platelet inhibition in poor metabolizers because such studies regarding variability of response could have "negative marketing implications." These facts and others outlined above lead this Court to find Defendants' conduct offended the established public policy of Hawai‘i.

102. Second, the Court also finds that Defendants conduct in this case was immoral, unethical, oppressive, or unscrupulous. The evidence showed that Defendants engaged in a pattern and practice of burying their heads in the sand regarding the weaknesses of Plavix. Regardless of the amount of evidence presented to Defendants (internally before launch of the drug, and later through repeated independent studies), they continued to deny the fact that there were Plavix poor metabolizers or that poor metabolizers received diminished or zero effect from taking Plavix. Such acts and practices were immoral, unethical and unscrupulous within the meaning of UDAP.

103. Finally, the Court also finds that Defendants' conduct was substantially injurious to consumers in several ways. First, Defendants deprived all patients of the opportunity to consider whether to undergo genetic testing in order to determine the likelihood that they would be able to bioactivate Plavix's antiplatelet effect. Second, they deprived all patients with CYP2C19 loss-of-function alleles the opportunity to make informed decisions regarding the potential risk of taking Plavix against the potential risks associated with alternative treatment. Third, they deprived an indeterminate number of patients the drug's intended risk reduction the patients were relying on Plavix to provide. Fourth, Defendants deprived patients the ability to give informed consent to their treatment.

II. DEFENDANTS' AFFIRMATIVE DEFENSES

104. Defendants raised in their Pre-trial Statement several affirmative defenses. However, Defendants did not argue all these defenses during trial or closing arguments. It is not clear whether Defendants have since abandoned some of these defenses. Out of an abundance of caution, the Court will discuss the reasons why each of these defenses are unconvincing.

A. First Amendment Defense

105. Defendants have asserted that the State's prosecution of this action violates their First Amendment commercial free speech rights. Defendants' theory appears to be that the State is attempting to punish them for refusing to disseminate the State's preferred message on a matter of scientific debate. The Court finds no merit to this defense. It is well established that "[t]he government may ban forms of communication more likely to deceive the public than to inform it, or commercial speech related to illegal activity." *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557, 563–64 (1980) (internal citations omitted). For commercial speech to receive First Amendment protections, "it at least must concern lawful activity and not be misleading." *Id.* Here, the Court has found that Defendants' omissions were deceptive and therefore the type of misleading statements not protected by the First Amendment.

B. Safe Harbor Defense

106. Defendants argued at trial that the statutory safe harbor provision codified in HRS § 481A-5(a)(1), bars the State's UDAP claim, which Defendants claim exempts "conduct in compliance with the orders or rules of, or a statute administered by, a federal, state, or local governmental agency." *Id.* Defendants posit that because the FDA repeatedly approved the Plavix label and never initiated any enforcement action against the Defendants related to Plavix, that Defendants' conduct was therefore at all times in compliance with the FDA regulations. The Court disagrees.

107. Under the terms of the FDA regulations, drug manufacturers can and must make necessary changes to a drug's prescribing information without seeking prior FDA approval. The FDA's periodic approval of Plavix label changes over the years does not place the Defendants "in compliance" with federal label regulation standards. The Court finds that Defendants are not immune from liability under the state's UDAP laws because their specific applications to update the label were approved. On the contrary, the Court finds that Defendants' conduct—failing to discharge their ongoing, affirmative duty to adequately inform patients—places them well outside the protections of the UDAP's Safe Harbor provision and well outside the ambit of "compliance" with orders, rules, or statutes administered by a separate governmental entity.

108. Through the FDA regulations, the FDCA provides drug manufacturers a specific mechanism for unilaterally strengthening warning labels after initially approved by the FDA. As the Supreme Court explained in *Wyeth,* "Congress did not . . . require[] the FDA to preapprove all changes to drug labels . . . Instead, it adopted a rule of construction to make it clear that

manufacturers remain responsible for updating their labels." *Wyeth,* 555 U.S. at 567-68. That responsibility is made enforceable through state law claims. *Id.* at 578-79. Both Congress and the Supreme Court recognize that state consumer protection laws, such as Hawaii's UDAP statute, play an important role in enforcing a manufacturer's duty to update their label. *Id.* In particular, the Supreme Court concluded that Congress "determined that widely available state rights of action provided appropriate relief for injured consumers" in connection with failure to warn claims related to FDA approved drugs. *Id.* at 574. Further, failure to warn actions under state law "lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA [has] long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Wyeth,* 555 U.S. at 579.

109. The Court finds that the Defendants' failure to update Plavix's label with material information was not conduct "authorized, permitted, or required by law." The responsibility for the adequacy of Plavix's drug label rested with Defendants, and Defendants were expressly empowered to fulfill that responsibility, but affirmatively chose not to out of fear that such disclosures would negatively impact their bottom line. As such, the Safe Harbor provision does not apply to Defendants' conduct in this case

C. Preemption Defense

110. In their trial brief, Defendants argued that the State's UDAP claim is preempted by federal law on prescription drug labeling and that the "relevant question is whether the FDA regulations allowed the [Defendants] to update the Plavix label before 2008 on its own, without first seeking the FDA's permission." To support this defense, Defendants informed the Court that during trial it would hear from their regulatory expert, Dr. Dena Hixon, who would explain, Defendants could not have unilaterally updated the label before 2008. However, during their defense case Defendants informed the Court that they would not be calling Dr. Hixon to testify. As such, the only evidence in the record regarding Defendants' ability to update the product label is the unchallenged and credible testimony of Dr. Plunkett. The Court therefore finds Defendants' preemption argument unsupported and unpersuasive.

D. Duty to Test

111. Defendants repeatedly argued at trial that evidence concerning their willful suppression of research is irrelevant because Hawaii's UDAP statute does not impose on

manufacturers any independent duty to conduct product testing or research. However, the State's allegations are not limited to the Defendants failure to conduct product testing or research. The State alleges Defendants ignored and concealed critical risk information concerning their drug, and then deliberately rejected and suppressed any further research into those risks, and in so doing, severely retarded the growth of pertinent scientific literature in the area of Plavix resistance and its causes, and the Court has so found. This conduct is part-and-parcel with Defendants' deceptive acts and practices, as it directly prevented correction of their material omissions.

112. Further, federal regulations require a drug's manufacturer to include in the labeling of its products complete and accurate information about health risks, adequate instructions regarding the use of the drug product, and adequate warnings to ensure that patient health is protected. *See*, *e.g.*, 21 CFR § 201.57; 21 CFR § 314.70; 21 CFR § 314.80. As such, manufacturers have the responsibility for ensuring that the labeling *continues* to reflect current knowledge concerning risks posed by the drug.

113. By failing to fulfill their duty to ensure Plavix's label reflected the current knowledge concerning risks posed by the drug, by deliberately shirking their obligation to conduct responsible postmarketing surveillance, by suppressing the efforts of concerned third parties to conduct postmarketing investigational studies, and by basing these critical decisions on sales and marketing concerns, Defendants engaged in unfair and deceptive practices that culminated in the material omissions at issue here.

III. PENALTIES

114. Based on the foregoing and the evidence presented at trial, the Court concludes that the imposition of civil penalties under HRS § 480-3.1 is warranted. The parties disagree on the way in which penalties should be calculated.

A. Penalties under § 480-3.1 are not Restricted to a "Per Day" Calculation as Posited by Defendants

115. Primarily, Defendants have argued before trial and during closing arguments that the calculation of penalties under HRS § 480-3.1 requires the court to calculate violations on a "per day" basis. The Court rejects Defendants' reading of the statute.

116. The relevant statutory provision, HRS § 480-3.1, states the following:

> Any person, firm, company, association, or corporation violating any of

> the provisions of section 480-2 shall be fined a sum of not less than $500 nor more than $10,000 for each violation, which sum shall be collected in a civil action brought by the attorney general or the director of the office of consumer protection on behalf of the State. The penalties provided in this section are cumulative to the remedies or penalties available under all other laws of this State. Each day that a violation of section 480-2 occurs shall be a separate violation.

117. In construing a statute, the Court's "foremost obligation is to ascertain and give effect to the intention of the legislature, which is to be obtained primarily from the language contained in the statute itself. And [the court] must read statutory language in the context of the entire statute and construe it in a manner consistent with its purpose." *Beneficial Hawaii, Inc. v. Kida*, 96 Hawai'i 289, 307, 30 P.3d 895, 913 (2001). "[W]here the terms of a statute are plain, unambiguous and explicit, [the Court is] not at liberty to look beyond that language for a different meaning." *State v. Haugen*, 104 Hawai'i 71, 76, 85 P.3d 178, 183 (2004). But where the language of a statute appears on the surface to be plain, obvious, and unambiguous, the court may look beyond that language "for the purpose of ascertaining its underlying legislative intent . . . if a literal construction would produce an absurd and unjust result." *Id*. at 77, 184 (internal citations and quotations omitted).

118. The UDAP statute "is remedial in nature and must be liberally construed in order to accomplish the purpose for which it was enacted." *Keka, supra*, 94 Hawai'i at 229, 11 P.3d at 17 ("Remedial statutes are liberally construed to suppress the perceived evil and advance the enacted remedy.") Therefore, this consumer protection statute "must be interpreted broadly in order to effectuate its remedial purposes." *Kida, supra*, 96 Hawai'i at 307, 30 P.3d at 913.

119. Applying a "per day" method of calculating penalties, as Defendants suggest, regardless of the circumstances of the deceptive or unfair act or practice is inconsistent with the plain language of the statute and would severely reduce its remedial power. Such a reading would also lead to absurd results and is inconsistent with similar cases under the Federal Trade Commission Act, 15 U.S.C. §§ 41-58 ("FTC Act").

120. First, the plain language of the statute shows the intent of the legislature to create a mechanism by which the State may hold those accountable who engage in deceptive or unfair practices. The first sentence of HRS § 480-3.1 states in unambiguous terms that a penalty "shall" be imposed "for <u>each</u> violation." (Emphasis added). This statutory language expresses a clear legislative intent that wrongdoers will be held accountable for <u>each</u> violation they commit.

Therefore the Court must first determine what constitutes a violation in order to assess a penalty. Defendants' interpretation—which would allow a wrongdoer to cap its liability to a maximum daily penalty of $10,000 no matter how many times it deliberately violated the statute in a single day—would only incentivize large and powerful corporations to violate Hawaii's consumer protection laws with impunity. A single daily penalty could easily just be absorbed as "the cost of doing business," or a "rounding error," and, even then, only *if* the perpetrators were caught and prosecuted.

121. The second sentence of HRS § 480-3.1 is consistent with the first in that it likewise expresses an intent to hold wrongdoers fully accountable for their actions by providing that the aforementioned civil penalties are cumulative of all other "remedies or penalties available under all other laws of this State." This provision does not suggest a legislative intent to let violators off lightly or limit the penalties available under this section, but rather to impose upon them the full weight of all applicable laws violated by the wrongful conduct.

122. The final sentence of HRS § 480-3.1 must be construed in a manner consistent with these first two sentences. First, the sentence reads: "Each day that a violation of section 480-2 occurs shall be a separate violation." By its own terms, this sentence does not define a violation but instead it modifies or multiplies the application of a violation if it is a continuing violation.

123. For example, there are some circumstances in which a single act can constitute a violation over a period of days without the violator having acted more than once, such as the posting of a deceptive billboard by the side of a highway. The offender would install the billboard only once, but the billboard would continue to have its deceptive impact every day until it was removed. Similarly, a court might issue an order for the offender to remove the billboard, but the offender might ignore the court's order. Although ignoring the order would be a single act, that single violation could continue for several days, until the offender eventually complied. In both examples, the third sentence of HRS § 480-3.1 would provide an appropriate remedy. It would not limit the violator's exposure to a single penalty but would instead impose a penalty on the violator for each day that the violation continued. The plain reading of the entire statute shows that this "each day" language was intended to act as multiplier not a limiter in the calculation of penalties.

124. Second, Defendants' reading of the statute so that penalties are restricted to a maximum of one "per day" would lead to absurd and unjust results. For example, suppose that 30,000 mail advertisements were distributed in a single day, which contained material determined to constitute unfair or deceptive acts or practices by the sender. Under Defendants' reading of the statute, these 30,000 advertisements sent to 30,000 separate consumers would constitute only one violation—because they were committed in a single day—with a ***maximum*** penalty of no more than $10,000, i.e., 33 cents per advertisement and deceived consumer. However, if 30 of these same unfair and deceptive advertisements were mailed—*one per day for thirty days* (1 month)—under Defendants' theory, that would constitute thirty separate violations with a ***minimum*** penalty of $15,000.

125. In the first example, the sender could make unfair and deceptive representations 30,000 times to 30,000 separate consumers, but if the representations were made in the same day, the sender would face a maximum penalty of $10,000, or 33 cents per advertisement. In the second example, the sender could make only 30 unfair and deceptive representations, but if the representations were made over the course of one month, one per day, the sender will face a maximum penalty of $300,000 – a thirty-fold increase over the other sender's maximum penalty – merely because the representations were made on separate days. Under Defendants' theory, the first sender would be subject to a maximum civil penalty that is $1/30^{th}$ the maximum civil penalty the second sender is subject to, despite having misled 29,970 more consumers than the second sender. Such an absurd result would not serve the purpose of the UDAP statute "to suppress the perceived evil and advance the enacted remedy." *Keka, supra*, 94 Hawai'i at 229, 11 P.3d at 17.

126. Third, courts in Hawai'i have routinely recognized that the purpose of statutes such as UDAP is to be a tool that can be used to combat deceptive and unfair practices in whatever iteration they exist. HRS § 480-2 was "constructed in broad language in order to constitute a flexible tool to stop and prevent fraudulent, unfair or deceptive business practices for the protection of both consumers and honest businesspersons." *Keka, supra*, 94 Hawai'i at 228, 11 P.3d at 16. UDAP cannot both be construed as a broad and flexible remedial statute for the purpose of protecting consumers while also construed to severely limit penalties so that any enforcement of the statute by the Attorney General would equate to a slap on the wrist for large corporations.

127. The plain language of the § 480-3.1 and the purpose of the UDAP statute show that the determination of what constitutes a "violation" of § 480-2 depends on the facts and circumstances of the case and the deceptive or unfair conduct at issue. Should a violation occur in a manner that a single violation extends over a period of multiple days, then the "each day" language may act as a multiplier to penalize the wrongdoer for the extended nature of the conduct. However, the determination of what counts as a violation still relies heavily on the circumstances of each case.

128. The Court's reading of the statute is further supported by targeted consumer protection statutes enacted by the Hawai'i Legislature – *i.e.,* laws *in pari materia*, HRS § 1-16 – that calculate violations based on the number of deceptive acts or practices of the violator. For instance, in HRS § 245-59, enacted in 2005, the Legislature declared that certain acts related to the sale of cigarettes constitute "unfair and deceptive practices" under § 480-2 and "shall be subject to civil penalty as provided in section 480-3.1." Section 245-59 then continues on, saying, ***[e]ach package of cigarettes sold*** in violation of this part shall constitute a separate violation." *Id.* (Emphasis added.)

129. Similarly, in HRS § 127A-30, enacted in 2014, the Legislature prohibits price increases during a state of emergency, and in those circumstances allows civil penalties under §480-3.1 because price gouging constitutes an unfair and deceptive practice. The statute further provides that *"**[e]ach item sold*** at a price that is prohibited by this section shall constitute a separate violation." HRS §127-30(e) (Emphasis added). These statutes clearly evidence a legislative intent in the consumer protection arena to define the number of violations based on the circumstances of the deceptive acts or practices at issue. Defendants argue that the above-cited statutes undercut the Court's reasoning because HRS § 480-3.1 does not have the equivalent of "each item" language in it, as the other statutes do. But this Court is not persuaded that Defendants' view is the correct one.

130. The above-cited statutes are each very narrowly tailored to address a single, discrete issue, such as price gouging or the sale of cigarettes. Therefore, specific "each item" or "each package" language could be added to those statutes with little difficulty. In contrast, UDAP is an extremely broad statute applicable to a virtually unlimited number of widely differing circumstances affecting consumers. Adding language that would properly fit all of those potentially innumerable circumstances would be impractical, highly problematic, and

likely impossible. *See e.g.*, *F.T.C. v. Sperry & Hutchinson Co.*, 405 U.S. 233, 240 (1972) ("It is impossible to frame definitions which embrace all unfair practices. There is no limit to human inventiveness in this field. Even if all known unfair practices were specifically defined and prohibited, it would be at once necessary to begin over again."). Therefore, the absence of such precise language in HRS § 480-3.1 is neither surprising nor indicative of any legislative intent to restrict the definition of a violation to specific verbiage applicable in all cases.

131. The Court's interpretation of the calculation of penalties under HRS § 480-3.1 is also consistent with federal case authority construing UDAP's federal counterpart, the Federal Trade Commission Act, 15 U.S.C. §§ 41-58 ("FTC Act").

132. In determining what constitutes a UDAP violation, HRS § 480-2(b) provides that "courts and the office of consumer protection shall give due consideration to the rules, regulations, and decisions of the Federal Trade Commission and the federal courts interpreting section 5(a)(1) of the Federal Trade Commission Act (15 U.S.C. 45(a)(1)), as from time to time amended." Federal case law calculating penalties under the FTC Act shows that the definition of a violation is defined based on unfair or deceptive conduct in each case. *United States v. Reader's Digest Ass'n, Inc. (Reader's Digest)*, 662 F.2d 955, 965–66 (3d Cir. 1981) (holding that "*each letter* included as part of a mass mailing constitutes a separate violation") (emphasis added); *United States v. J. B. Williams Co.*, 498 F.2d 414, 435 (2d Cir. 1974) (holding that "*each separate broadcast* of [a] commercial was a separate violation" rather than each day the commercial aired) (emphasis added); *United States v. Floersheim*, No. CV 74-484-RF, 1980 WL 1852, at *9 (C.D. Cal. May 1, 1980) (holding that *"[e]ach individual form* [containing the misrepresentations] constitutes a separate violation") (emphasis added); *accord State ex rel. Wilson v. Ortho-McNeil-Janssen Pharmaceuticals, Inc.*, 414 S.C. 33, 84-85 (2015) (upholding that "distribution of *each sample box* containing the deceptive labeling, *each [Dear Doctor Letter]*, and *each follow-up sales call* to the DDL by a Janssen representative constituted a separate . . . violation") (emphasis added).

133. Further, under the FTC Act, the "each day" calculation is reserved for circumstances in which there is a "continuing failure to comply with a rule or with [§ 45(a)(1).]" 15 U.S.C. § 45(m)(1)(C). It is therefore appropriate to construe the "each day" provision in HRS § 480-3.1 as a clarifying sentence that compounds the penalty on a daily basis for a single

violation that continues to have an impact over a number of days, rather than as a limiting factor on the calculation of civil penalties.

134. As such, the Court rejects Defendants' reading of § 480-3.1 as requiring the Court to calculate penalties in terms of one violation per day. Instead, the Court will analyze the facts and circumstances of this case and determine the appropriate definition and number of violations based on the evidence presented at trial.

B. Factors to Consider in Penalties Calculations

135. Courts exercising discretion in determining the measure of penalties to be assessed under the FTC Act or similar state consumer protections statutes utilize the factors articulated in *United States v. Reader's Digest Ass'n (Reader's Digest)*, 662 F.2d 955, 967 (3rd Cir. 1981):

(1) The good faith or bad faith of the Defendant;

(2) The injury to the public;

(3) The desire to eliminate the benefits derived by a violation;

(4) The necessity of vindicating the authority of the agency involved; and

(5) The Defendant's ability to pay.

See State ex rel. Wilson v. Ortho-McNeil-Janssen Pharmaceuticals, Inc., 414 S.C. 33, 84-85, 777 S.E.2d 176, 203 (2015); *U.S. v. Natl. Fin. Services, Inc.*, 98 F.3d 131, 140 (4th Cir. 1996); *U.S. v. Gurley*, 235 F. Supp. 2d 797, 806 (W.D. Tenn. 2002), *aff'd*, 384 F.3d 316 (6th Cir. 2004); *U.S. Dept. of J. v. Daniel Chapter One*, 89 F. Supp. 3d 132, 148 (D.D.C. 2015). Here, the Court considers each of these factors in turn in determining the civil penalties to impose on Defendants.

i. Good or Bad Faith of Defendants

136. The Court finds that the Defendants acted in bad faith during the relevant period of 1998 to March 2010. As discussed above, the law allowed Defendants to unilaterally strengthen the warning section of the drug label as soon as there was reasonable evidence of a safety issue with their drug. Nothing in those regulations required a showing of any sort of association of "clinical outcomes" before making such updates, as Defendants argued. Defendants had knowledge of the involvement of CYP2C19 in the metabolism of Plavix, and the ability of its polymorphisms to prevent activation of other prodrugs, as well as Plavix's own issues with variability of response as early as 1998, before the drug was ever sold on the market. Yet Defendants ignored these glaring warning signs and did nothing to warn patients or

physicians, nor did Defendants investigate the reasons for this resistance. Further, Defendants systematically, through policies and guidelines, suppressed studies of Plavix resistance and avoided documenting variability of response due to perceived threats to sales and potential negative marketing implications.

137. Even after Key Opinion Leaders began discovering the issue of variability of response, Defendants continued their obfuscation campaign and refused to fund or run the type of clinical studies that could have answered the questions about variability of response that Key Opinion Leaders and other researchers continued to ask. Once the medical community—without the aid of Defendants—performed research showing the links between the 2C19 loss-of-function alleles and lack of platelet response, Defendants did not update their label or run a large-scale trial investigating this genetic link. Instead, Defendants buried their heads in the sand and continuously maintained that the 2C19 polymorphism was not linked to "clinical outcomes" as a self-serving excuse to avoid addressing the problem.

138. From 1998 to March 2010, Defendants had the ability and knowledge necessary to update the Plavix drug label. Yet, they chose not to because it would affect their bottom line. Defendants repeatedly chose to act in their own financial best interest rather than fulfilling their obligations with respect to patient safety. Therefore, the Court finds Defendants' bad faith to be considerable during the period of December 1998 to March 12, 2010.

ii. Injury to the Public

139. The Court finds the issues in this case to be of critical importance to the public. Requiring drug manufacturers to fully disclose all material information available to them concerning the safety of their drugs in a fair and non-deceptive manner is of paramount importance to the health and safety of those using the drugs. This is especially true where, as here, the drug at issue is a potentially lifesaving course of therapy, and where a patient's failure to fully bioactivate the drug leaves them more vulnerable to heart attacks, strokes, and cardiovascular death. Doctors and patients can only make fully informed decisions regarding treatment when a complete, honest, and fair disclosure of material information is made by the drug manufacturer. As drug manufacturers are the ones with the best and most complete information surrounding their drug, the public must be able to rely on these companies to disclose important information, such as lack of efficacy based on genetic factors. Injury to the public obviously occurs when consumers are denied material information that is necessary for

them to make informed decisions concerning their course of treatment and when the risk of a recurrent heart attack or stroke is not lowered as represented by the drug manufacturer. As such, the public interest affected by Defendants' actions in this case is substantial.

iii. Desire to Eliminate the Benefits Derived from a Violation

140. The benefits derived by Defendants' material omissions were substantial. After its launch in 1998, Plavix became a "blockbuster drug" and prescribing Plavix in addition to aspirin became the standard of care for treatment of many cardiovascular related conditions. We cannot turn back the clock to see what would have happened had the label included adequate warnings from the beginning. Nonetheless, it is clear from the revenue generated by Defendants, discussed below, that Defendants were able to reap huge financial benefit from the success of Plavix, including from the consumers within the State of Hawai‘i, while using unfair and deceptive practices to do so. Moreover, the evidence at trial clearly established that Defendants themselves feared the loss of Plavix sales and questions from health authorities should the limitations of their drug be documented. The civil penalty calculations therefore must also account for the need to eliminate the benefits derived by Defendants from their use of unfair and deceptive business practices.

iv. Necessity of Vindicating the Authority of the Agency Involved

141. The UDAP statute was enacted by the legislature to act as a consumer protection measure and under § 480-3.1 the State, through its Attorney General, was given power to enforce those protective measures for the people of Hawai‘i. When corporations or other business entities come into this State and conduct their business in an unfair and deceptive manner, it is incumbent upon the Attorney General as the chief law enforcement officer of the State to act in protection of the public's interest. Remedial statutes, such as UDAP, are to be construed "to suppress the perceived evil and advance the enacted remedy." *Keka, supra*, 94 Hawai‘i at 229, 11 P.3d at 17.

142. The Court finds that the State has a particularly strong interest in ensuring that drug companies operate legally in Hawai‘i and are not making false statements about pharmaceutical drugs to the public, especially when it comes to potentially life-saving drugs like Plavix. The State's interest is heightened where, as here, the omission of warning information

raises a serious risk of harm to all consumers, but especially to high risk patients of East Asian and Pacific Island descent, who represent a significant portion of Hawaii's population.

143. As such, the penalties imposed in this case will take into account the interests of the State in preventing similar acts and practices in the future.

v. Defendants' Ability to Pay

144. Here, it is important to consider what penalties are necessary for Defendants to fully appreciate the wrongfulness of their conduct and to deter them from taking similar actions in the future. To achieve that goal, the penalty must take into consideration the financial ability of the wrongdoer to pay. As the primary purpose of statutes such as UDAP are to protect consumers and deter future unfair or deceptive conduct by Defendants and others, the penalty must be of an amount that is appropriate for each particular defendant involved. If a penalty is more than a defendant can pay, then justice would not be served. Similarly, if a penalty is so small that it can be written off as a mere cost of doing business, then consumers would not be adequately protected. The legislature has already determined what constitutes the fair range of penalties per violation under § 480-3.1: between $500 and $10,000. Therefore, the Court must determine an amount within that range.

145. Defendants in this case are large multinational corporations with very substantial resources. As shown by Defendants' financial filings with the SEC for years 1998 through 2012, Defendant BMS reported net sales of Plavix totaling $50.3 billion. In the financial filings with the SEC for years 2002 through 2012, Defendant Sanofi reported net sales from Plavix totaling €22.1 billion.[9] Therefore, Defendants have the ability to pay an award appropriate to the egregiousness of their misconduct toward Hawai‘i consumers.

C. What Constitutes a Violation

146. As discussed above, the Court finds that Defendants' unfair and deceptive conduct in this case was far reaching and persistent. Based upon the evidence presented at trial and the above Findings of Fact, the Court finds that a violation of UDAP occurred with the distribution of each copy of the Plavix label (package insert), by way of retail prescriptions filled (including refills) and non-retail units sold, in the State of Hawai‘i.

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[9] These sales figures do not include numerous other drugs, from which each Defendant has also generated billions of dollars in sales, according to the SEC filings in evidence.

147. Tallying the number of violations in terms of the retail prescriptions filled and non-retail units sold is appropriate given the circumstances of the unfair and deceptive acts in this case. The warnings, risks, and benefits listed in a drug's label are a cornerstone to the patient's ability to make an informed decision regarding that drug. The "Medication Guide" portion of Defendants' own label instructs patients to read the label before they "start taking Plavix and each time [they] get a refill." The label also notes that the information in the boxed warning is "the most important information [you] should know about Plavix[.]" This Medication Guide is required by law to be included with the drug label in every unit (retail and non-retail) of Plavix. As such, the Court finds that each retail prescription filled and refilled, and non-retail units sold in the State of Hawai'i constitute a separate and distinct violation of UDAP.

148. The Court finds Defendants' arguments about reducing the number of violations unconvincing, as well as unsupported by the law or evidence presented in this case.

D. Number of Violations and Penalty Amount

149. Given the evidence presented at trial, the above Findings of Fact, and the above Conclusions of Law, this Court finds that each retail prescription filled and refilled, and each non-retail unit sold in the state of Hawai'i by Defendants, between December 1998 and March 12, 2010 to be a separate UDAP violation. Defendants argued briefly in closing arguments that the time period for calculations should be limited to the date of publication of either (1) the research paper published by Jessica Mega in November 2008 (which Defendants contend first showed the prevalence of CYP2C19 in Plavix metabolism), or (2) the paper published by Jean Sebastian Hulot in 2006 (which was an independent research study showing the link between CYP2C19 poor metabolizers and poor responders). The Court is not persuaded by these arguments. As discussed above, the overwhelming weight of the evidence is that Defendants' unfair and deceptive business practices extended back to the launch of Plavix in December 1998. As such, the Court finds that the number of violations of UDAP resulting from the Defendants' joint misconduct is **834,012**, as calculated by the State's expert Dr. Nicole Maestas, which went unchallenged.

150. The Court further finds the appropriate penalty to be $1,000 per violation, for a total of **$834,012,000.00** in civil penalties.

151. Under Hawai'i law, the Court acknowledges that the penalties under HRS § 480-3.1 may not be assessed jointly and severally against distinct legal entities except where several

entities are subject to a single control, such as in the corporate parent-subsidiary relationship. *State by Doi v. Shasteen*, 9 Haw. App. 106, 113, 826 P.2d 879, 883 (1992). While Sanofi and Bristol-Myers Squibb acted jointly in their venture of selling Plavix between December 1998 and March 12, 2010, the Court finds that they are legally separate entities. On the other hand, the Court finds that defendants Sanofi-Aventis U.S. LLC, Sanofi US Services, Inc., and Sanofi-Synetholabo LLC are all entities under a single control and thus shall be considered one legal entity for purposes of penalty assessment. Therefore, the Court will assess one set of penalties against Bristol-Myers Squibb and one set of penalties jointly and severally against the Sanofi defendants.

152. At no point has any party in this trial argued or presented evidence that either Bristol Meyers Squibb or Sanofi were more or less culpable than the other in engaging in the unfair and deceptive business practices at issue. As such, the Court finds that Bristol-Myers Squibb and the Sanofi defendants are both equally responsible for each violation of UDAP in this case and, therefore, assesses civil penalties in the amount of **$417,006,000** against Defendant Bristol-Myers Squibb Company and civil penalties in the amount of **$417,006,000** jointly and severally against Defendants Sanofi-Aventis U.S. LLC, Sanofi US Services Inc., and Sanofi-Synthelabo Inc.

153. The Court considers the foregoing award of civil penalties to be an adequate remedy for Defendants' wrongful conduct. Therefore, the Court finds it unnecessary to determine whether the circumstances of this case might otherwise warrant either an award of punitive damages or the remedy of disgorgement.

154. If any of the Conclusions of Law set forth herein shall be deemed instead to be Findings of Fact, they are hereby incorporated by reference in the Findings of Fact set forth herein above.

DECISION AND ORDER

IT IS HEREBY ORDERED, ADJUDGED AND DECREED that judgment shall be entered in favor of Plaintiff State of Hawai‘i and against Defendants Bristol-Myers Squibb Company, Sanofi-Aventis U.S. LLC, Sanofi US Services Inc., and Sanofi-Synthelabo Inc. in the

amount of $834,012,000.00, to be assessed against each of the Defendants in the manner described above.

This document shall be filed in the State of Hawaii Judiciary electronic portal and distributed to counsel for the parties via email.

DATED: Honolulu, Hawai‘i, February 15, 2021.

/s/ Dean E. Ochiai

JUDGE OF THE ABOVE-ENTITLED COURT