IN THE CIRCUIT COURT OF THE FIRST CIRCUIT

STATE OF HAWAI‘I

STATE OF HAWAI‘I, EX REL. ANNE E. LOPEZ, 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. 1CC141000708 (JHA) (Other Non-Vehicle Tort) **FINDINGS OF FACT, CONCLUSIONS OF LAW, AND ORDER** Trial Date: September 25, 2023 – October 16, 2023 Trial Judge: Honorable James H. Ashford

INTRODUCTION

This is a partial retrial of 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 Defendants**," 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 and sold 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 (hereinafter "**diminished response**" or "**resistance**"), due in part to the prevalence of genetic variants ("**polymorphisms**") in the patients' hepatic (liver) enzymes. The State asserts that Defendants engaged in these alleged unfair or deceptive acts or practices from the time 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.

[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]

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. However, the State only sought penalties under HRS § 480-3.1 during this trial and expressly waived the other claims and remedies at closing argument.

This matter was originally tried before the Honorable Dean E. Ochiai (hereinafter "**original trial court**") without a jury over a period of four weeks in October and November 2020. On February 15, 2021, the original trial court issued its Findings of Fact, Conclusions of Law, Decision and Order [Dkt. No. 1373], finding, in sum, that Defendants had acted both unfairly and deceptively toward Hawai'i consumers, in violation of Hawaii's UDAP statute, with respect to all retail and non-retail Plavix prescriptions filled and/or refilled between launch of the product in December 1998 and the March 2010 announcement that an FDA-mandated boxed warning would be added to the Plavix label.

The original trial court's unfairness and deceptiveness findings were based upon, among other things, Defendants' failure to investigate information in their possession regarding Plavix resistance, suppression of research, "burying their head in the sand" regarding the resistance issue, and failing to update their Plavix label to warn about the risk of Plavix resistance. Dkt. No. 1373 at 28 and 30-31.

The original trial court found that 834,012 prescriptions were filled or refilled during that period and that each of those fills or refills were violations of Hawaii's UDAP statute because the package insert (label) for each fill and refill omitted material information and was deceptive. *Id.* at 41-42. The original trial court determined that an appropriate per-prescription penalty for

each UDAP violation was $1,000, with half the amount allocated to BMS and half the amount allocated to the three Sanofi Defendants, jointly and severally. *Id.*

On appeal, the Supreme Court of Hawai‘i affirmed in part and reversed in part the original trial court's judgment, remanding this case for a partial retrial. The Supreme Court affirmed the original trial court's judgment as to the State's unfairness claims, finding "defendant companies' conduct offended public policy" and Defendants "behaved in an 'immoral, unethical, oppressive, unscrupulous' manner." *State of Hawai‘i ex rel. Shikada v. Bristol-Myers Squibb Co. ("Shikada")*, 152 Hawai‘i 418, 447, 448, 526 P.3d 395, 424, 425 (2023). In so doing, the Supreme Court cited specific "findings [that] support the court's unfair acts decision," *Shikada*, 152 Hawai‘i at 448, 526 P.3d at 425:

- Defendants "aimed to avoid their common law duty [to warn consumers when a drug's risks become apparent] by: suppressing research and continuously and repeatedly failing to further investigate the risks of reduced platelet inhibition in poor metabolizers" *Id.* at 447, 526 P.3d at 424.
- "the companies knew—from the moment Plavix launched—about the diminished effects of Plavix in non-White populations" and "the companies did not volunteer this information to the FDA." *Id.*
- "the companies avoided funding studies which could draw more attention to the variability of response, for instance, by rejecting a study on aspirin resistance because 'it could lead to a similar trial on [Plavix] resistance.'" *Id.*
- "[t]he companies' actions . . . set back the research into CYP2C19 by consciously, repeatedly, and actively avoiding the poor responder problem . . . to avoid 'negative marketing implications' for Plavix." *Id.*
- "the companies prioritized profits over patients: defendant companies 'buried their heads in the sand' about the problems with Plavix to protect the corporate bottom line." *Id.* at 448, 526 P.3d at 425.
- "the companies 'continued to deny' the issues surrounding poor response to the drug despite evidence to the contrary, giving the impression that no one had any reason to be alarmed" *Id.*

Independent and regardless of the original trial court's findings and the Supreme Court's findings, the Court also finds that the factual determinations stated in the above six bullet points were equally and independently supported by the evidence presented during the current retrial of this case and independently hereby finds these as facts.

However, the Supreme Court held that it was error for the original trial court to grant partial summary judgment regarding the materiality of the information Defendants omitted from their label, and this error impacted several different aspects of the original trial court's decision.[2] First, the Supreme Court concluded the premature materiality ruling denied Defendants a trial on two essential elements of Plaintiff's deception claim, materiality and tendency to mislead, thereby requiring a new trial on the State's deceptive practices claim. *Shikada,* 152 Hawai'i 443, 526 P.3d 420. Second, the Supreme Court also vacated the original calculation of penalties because the original trial court heavily relied "on its materiality ruling to reach its penalties determination." *Id.* After remand, the case was assigned to this Court.

This Court commenced trial on Monday, September 25, 2023, and concluded on Monday, October 16, 2023. As set forth in detail below, the Court finds in favor of the State and against Defendants for the relief set forth herein. Having considered all of the evidence submitted at trial, the credibility of each witness who testified—as well as the foundation for each witness's

[2] The Supreme Court also overturned the original trial court's conclusion that Defendants caused substantial injury under UDAP's unfairness prong because that determination was also influenced by the premature materiality ruling. *Id.* at 444, 526 P.3d at 421. However, because the unfair practices holding was supported on other, independent grounds, the Supreme Court affirmed the unfairness liability judgment. *Id.* at 445-48, 526 P.3d at 422-26. The Supreme Court stated, therefore, that on remand, "there will be no second trial on the unfair acts or practices claim." *Id.* at 423, 526 P.3d 400.

testimony and the foundation for all evidence received—and being fully informed, the Court makes the following findings of fact and conclusions of law:

FINDINGS OF FACT

1. Plavix, whose generic name is clopidogrel bisulfate (hereinafter "**Plavix**" or "**clopidogrel**"), is an oral antiplatelet medication in tablet form. P0409 at 16 [Plavix 1997 label].[3] "**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. 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. This is especially true for patients who have had metal stents placed in their arteries for the purpose of revascularization, via a procedure called "**percutaneous coronary intervention**," or "**PCI**," in which clots can both form and cause fatal blockages. The purpose of antiplatelet medications like Plavix is to reduce the risk of such recurrent adverse events by inhibiting platelet aggregation.

3. Plavix was developed, manufactured, and placed into the prescription drug marketplace by BMS and Sanofi Defendants. P0409 at 16 [Plavix 1997 label].

4. 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

[3] In this document, Plaintiff's trial exhibits are identified as "P____." Defendants' Exhibits are identified as D____."

patient's liver ("**hepatic enzymes**"), but sometimes by enzymes elsewhere in the patient's body or other mechanisms of action.[4] If, for any reason, the patient's body fails to bioactivate the prodrug, [5] it is effectively a placebo and remains inert within the body until it is eliminated, 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.

5. Plavix is a prescription drug, and like all prescription drugs its marketing, sale, and prescription are subject to regulation by the FDA. The FDA determines the approved uses (indications) to which a prescription drug may be used, and under what circumstances it may be prescribed. The FDA also issues regulations that impose various obligations on a drug manufacturer regarding labeling and marketing of a drug, as well as post-market surveillance of a drug to detect new or more serious problems with the drug than were detected during the clinical and preclinical trials leading up to FDA approval.

6. 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

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

[5] 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.

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, which 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 human use and for the indication that will be on the drug's label. Phase III studies are large, usually thousands of patients, and are complex and expensive to perform. 21 CFR 312.21.

7. The Phase III trial for Plavix involved a combined head-to-head comparison of Plavix to aspirin for the treatment of three different cardiovascular conditions, myocardial infarction ("**heart attack**"), ischemic stroke, and PAD. The trial is known by the acronym "**CAPRIE**" (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events). P0551 [CAPRIE Final Study Report – Internal].

8. In CAPRIE, Plavix was compared to aspirin because aspirin is also an antiplatelet medication. *Id*. Aspirin has proven effective in reducing cardiovascular events in patients with a recent heart attack or stroke. From 1997 and on, aspirin was considered the standard of care antiplatelet agent for prevention of arterial thromboses. D1735 at 12 [CAPRIE Protocol].

9. The results of the CAPRIE study showed Plavix had only a marginal overall benefit over aspirin across the three cardiovascular conditions studied. P0551 at PLAV_SAN_01648982 [CAPRIE Final Study Report – Internal].[6] For patients who enrolled in the trial on the sole basis of a recent heart attack, Plavix was numerically inferior to aspirin. The

[6] *See*, *also*, P0472 at bates ending 990 [Blumenthal email, 2007] ("[E]ven in CAPRIE (essentially the only trial of [clopidogrel] vs. [aspirin]), the benefit of [clopidogrel] over [aspirin] is marginal at best . . .")

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 significant than aspirin for those who had recently suffered a heart attack (-4.0%). *Id.* at PLAV_SAN_01648999. As a result, Plavix was not approved for the primary prevention of a 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. P0409 at 7 [Plavix 1997 label]. This approval was issued on November 17, 1997. *Id.*

10. 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. P0021 at PLAV_SAN_01648849 [9/5/91 Letter from FDA]. Yet, when the study was conducted Defendants included only 5% non-Caucasians. P0551 at PLAV_SAN_01648972 [CAPRIE Final Study Report – Internal]. Nevertheless, as relevant here, the CAPRIE trial did detect a statistically significant disparity in the number of adverse events suffered by non-white racial groups. *Id.* at PLAV_SAN_01649007 ("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…."). Dr. Dominique Roome, a former practicing and medication prescribing physician and a former employee of Sanofi, testified that this finding raised a red flag that required further investigation. The Court agrees and so finds.

11. This racial disparity in the response to Plavix was contained in Defendants' January 13, 1997 *internal* report of the CAPRIE study (hereinafter "**CAPRIE Report"**). *Id.*. However, the medical article about the results of that internal trial that was released by Defendants' Plavix Steering Committee for publication to the broader medical community

(hereinafter "**CAPRIE Article**") omitted any mention of this statistically significant racial disparity. D1078 [CAPRIE Published Article]. As a result, outside scientific researchers were denied this important information, which likely impeded the evolution of the science in this area.

12. In February of 1997, 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. P0225 at PLAV_BMS_0063805 [MIH0012 Internal Study Report].

13. In March of 1998, after FDA approval but prior to Plavix's launch into the commercial market, Defendants completed a meta-analysis of internal data regarding Plavix (hereinafter "**1998 Meta-Analysis**"). P0037 [1998 Meta-Analysis]. The 1998 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**"). *Id.* at PLAV_SAN_01569368.

14. This 1998 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 Defendants), in which the information was given within hundreds of pages into an appendix of another document. 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.

15. 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. P0226 at PLAV_PP_BMS00110067, PLAV_PP_BMS00110083 [MIV0265 Internal Study Report].

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

17. In their attorney's opening statement, Defendants asserted 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 argued that science evolves, and therefore their failure to include information they did not know cannot be unfair or deceptive. However, several of Defendants' witnesses (i.e., Dr. John Kao, Tony Hebden, and Brian Gavin) conceded, and the Court finds, that science only evolves if you do the research. Court's Exhibit F (10/11/18) at 38:11-39:4 [Gavin]; Court's Exhibit C at 159:15-160:19 [Hebden].

18. In addition to the results of the 1998 Meta Analysis, Defendants knew at least the following at the time of launch:

a) Plavix is a prodrug (P0225 [MIH0012 Internal Study Report]);

b) Plavix is bioactivated by enzymes in the patient's liver (*id.*);

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) (*id.*);

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 (*id.*; P0226 [MIV0265 Internal Study Report]);

e) CYP2C19 is and was known to be genetically polymorphic, i.e., it had several different variant forms, some of which might potentially be able to

activate a prodrug and some of which might not (P0444 [De Morais, 1994]; P0264 [De Morais,1994]);[7]

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

g) in other drugs known to be metabolized by CYP2C19, the polymorphisms of CYP2C19 had been shown to be less effective or to have no effect in activating the drug (P0444 [De Morais, 1994]; P0264 [De Morais, 1994]);

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 prodrug named S-mephenytoin (P0444 [De Morais, 1994]; P0264 [De Morais, 1994]);

i) the team of researchers who demonstrated the adverse effect of CYP2C19 polymorphisms on the metabolism of S-mephenytoin (hereinafter "**de Morais Team**") developed a simple PCR-based laboratory test to identify the CYP2C19 gene and its genetic polymorphisms (P0444 [De Morais, 1994]; P0264 [De Morais, 1994]);

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 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." (D1098, at 4 [De Morais, 1994]);

[7] 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 an 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 (P0444 [De Morais, 1994]; P0264 [De Morais, 1994]);

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 metabolize the drug (S-mephenytoin) (P0264 [De Morais, 1994]) and 100% of Chinese subjects (P0305 [De Morais, 1995]);

n) there was a group of poor responders to Plavix (P0037 [1998 Meta-Analysis]); and

o) Plavix patients who are poor responders, and therefore do not receive the intended antiplatelet effect, are likely at a higher risk of a recurrent heart attack or stroke than those who are not poor responders.

19. The lack of a uniform patient response to Plavix of the kind that was revealed by the 1998 Meta-Analysis was first called "**Plavix resistance**."[8] Given the potential severity of the

[8] The concept of Plavix resistance has been renamed—by Defendants—over the years a number of times for marketing purposes to terms such as Variability of Response ("**VOR**") and Variability of Platelet Response ("**VPR**"). *See e.g.*, P0610 at PLAV_BMS_00559949 [LCM/DC Achievements in 2003]; P0430 at PLAV_BMS_00608286 [2005 Competitive Workstream

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 it was "important [to] identify[] potential interindividual differences in metabolism and/or clearance due to genetic polymorphism." P0225 at PLAV_BMS_00663794 [MIH0012 Internal Study Report]. Defendants further noted that "[t]he use of *in vitro* methods has been recommended to investigate these issues[.]" *Id.* Further, Defendants' witness, Brian Gavin, testified that during the early years of Plavix's sales, Defendants knew that "if one of the redundant pathways was affected, that might have an impact on the generation of the active metabolite." Court's Exhibit F, 02/03/23 at 49:20-50:15 [Gavin].

20. Despite this acknowledgement and Defendants' awareness that: (1) they did not know precisely how Plavix was bioactivated; (2) CYP2C19 played a primary role in the bioactivation of Plavix; (3) CYP2C19 was genetically polymorphic and its polymorphic nature prevented the activation of other drugs; (4) CYP3A4 did not have a known loss-of-function genetic polymorphism that impaired patients' metabolism and pharmacodynamic responses to drugs; (5) Defendants' own 1998 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

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Meeting Notes]. Plavix resistance also encompasses the concepts of poor metabolism and poor response. These terms may be used interchangeably throughout these findings and conclusions.

FDA's or the public'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 the risks associated with Plavix resistance. Instead, Defendants, through their conduct and words over many years, clearly showed that their unmistakable intent was to not conduct or sponsor any research that could confirm the existence or causes of Plavix resistance.

21. One of the State's medical and regulatory experts, Dr. Laura M. Plunkett ("**Dr. Plunkett**"), presented testimony that Defendants were obligated to update their label to include a warning or precaution concerning the risk to poor metabolizers based on information brought to light by Defendants' 1998 Meta-Analysis, coupled with Defendants' knowledge that CYP2C19 was one of three principal enzymes involved in the metabolism of Plavix. Dr. Plunkett also testified that drug companies should be the primary entity investigating potential problems with their own drugs to ensure their label contains all the warnings and information necessary for the safe and effective use of Plavix. The Court agrees with Dr. Plunkett with respect to the two preceding sentences and so finds. Dr. Plunkett's testimony is consistent with the words of the Supreme Court of Hawai'i, which held: "Pharmaceutical companies have a common law duty to warn consumers 'when the risks of a particular drug become apparent.'" *Shikada*, 152 Hawai'i at 447, 526 P.3d at 424, quoting *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1677 (2019). Dr. Plunkett's regulatory and pharmacological opinions went unrebutted at trial, as Defendants presented no counter expert on either topic.

22. 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, and despite their knowledge that CYP2C19 was one of three principal enzymes involved in the metabolism of Plavix and was polymorphic, 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 demonstrate an intent to avoid pursuing these issues. In many instances, Defendants' 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.

23. Broadly speaking, the Court finds Defendants' internal emails that were authored long before this lawsuit was filed to be far more telling and probative than much of the trial testimony offered by Defendants' past and current employees. Additionally, the Court finds Defendants' past and present employees to often have little credibility on the facts and issues most important in this case. As a broad generalization, the Court was repeatedly unfavorably impressed with the avoidance and obfuscation by Defendants' past and present employees' testimony at trial. The Court's findings of fact are informed to a large degree by the sentiments expressed in this paragraph.

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

25. During trial, Defendants attempted to justify and defend their inaction and suppression of studies. The Court is not persuaded by Defendants' efforts.

26. Defendants' representatives testified and 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 Defendants' claim that they did not discover the cause of the poor response by non-Caucasians reflected in the CAPRIE study or 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, which prove that Defendants were aware of the risks associated with Plavix resistance from the moment Plavix launched and that Defendants had a clear intent to avoid any studies that might unearth negative information about Plavix.

28. For example, in May of 2000, BMS's medical director (Mel Blumenthal) proposed supporting a clinical trial to examine response to the drug in "blacks vs. whites" and noted "such a trial would be small, easy to do, and could be done well in time." P0603 at PLAV_JPP_BMS01136522 [Bouthier Email Chain May 2000]. However, Dr. Blumenthal's 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." *Id.* Sanofi further warned that such a study "could bear significant risk." *Id.* Dr. Roome agreed in her testimony that, based on the CAPRIE study showing a statistically significant difference in race, Defendants needed to further investigate the issue. When asked whether the distinction in responsiveness between Blacks vs. Whites was ever studied, Dr. Roome admitted that Defendants did not do any such study.

29. Further, Defendants internally noted they "had difficulty mobilizing the LCM (**Life Cycle Management Committee**) to address the importance of understanding Plavix resistance through [their] data and proactive research." P0566 at PLAV_JPP_BMS00805251 [Reddick Email June 10, 2003]. This statement of policy was particularly significant considering

Defendants' earlier observation in the CAPRIE Report of "a statistically significant interaction between treatment and race." [9] P0551 [CAPRIE Final Study Report - Internal].

30. Defendants' current and former employees testified at trial that the LCM's dismissal of studies was not the end of the analysis because the real studies were being done at the corporate level. However, Defendants' documents betray those assertions. While strategizing to obtain a commercial advantage over a competitor's drug, Defendants noted in an internal planning memo that "[a]dditional studies needed; can be small trials to help us to 'shape the debate." P0430 at PLAV_BMS_00608286 [2005 Competitive Workstream Meeting Notes]. As such, the claim that local studies were somehow less valuable than corporate studies is undermined by Defendants' own words. Further, the Court finds there were no studies at the corporate level or at any level that adequately studied the issues of Plavix resistance or the people affected by it.

31. 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 at

[9] At trial, Defendants introduced testimony of current and former executives that the Life Cycle Management Committee 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 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 Dr. Gurbel explained persuasively that the larger studies that Defendants did conduct or sponsor were not designed or powered to resolve the Plavix resistance issue, or the role of CYP2C19 in the bioactivation process, or the impact of race on Plavix resistance. Additionally, all of the corporate studies Defendants identified during trial as representing their efforts to study these issues, were identified contemporaneously by Defendants themselves as failing to be "adequately sized to detect difference in outcome in poor metabolizers." P0835 at PLAV_JPP_BMS00686475 [Stanton Email April 14, 2010].

PLAV_PP_BMS00419339 [LCM/DC Minutes June 21, 2001]. 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 at PLAV_PP_BMS00509530, -581 [LCM/DC Achievements in 2002].

32. 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 [Ogletree Email October 19, 2002]. 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 Defendants but unknown to the public, the FDA, or the scientific community.

33. In 2002, a study conducted by researchers not affiliated with Defendants, Järemo et al., was published that reflected resistance to Plavix among 28% of the patient population. P0259 [Järemo, 2002].

34. In 2003, several important studies were published. One study was conducted by the State's medical/clinical research expert, Dr. Gurbel, which found "[t]here was marked interindividual variability in drug response" in upwards of 31% of the patient population." P0255 [Gurbel, 2003]. At the time, Defendants praised Dr. Gurbel as important and brilliant. And for many years thereafter, Defendants considered him "the [world-wide] expert on VPR." P0583 [Roome Email July 13, 2006].

35. Subsequent studies published that year confirmed Dr. Gurbel's findings. Nevertheless, Defendants' internal records noted they "remain[ed] adverse to doing any further research on either aspirin—or [Plavix]—resistance because of the potential negative marketing implications." P0569 [Gavin Email Chain June 11, 2003]. 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 employee to note that "[t]here doesn't appear to be a high sense of urgency around this on their [Sanofi's] side." P0567 [Yost Email Chain June 11, 2003]

36. In 2004, Defendants continued rejecting clinical trials and made it a blanket policy that "any studies based on clopidogrel resistance hypothesis" were trials that "can not [sic] be done" (P0030 at PLAV_PP_BMS00279637 [Local Trials Implementation Guide]), despite their own determination that it was logical to conclude the variability in response had clinical consequence.

37. 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."[10] P0429 at PLAV_JPP_BMS01464236 [AHA Summary, 2005].

38. In June of 2006, a clinical study conducted by researchers not affiliated with Defendants confirmed a clear association between genetic polymorphisms in patient CYP2C19 liver enzymes and Plavix variability of response, sometimes referred to as VOR. D1194 [Hulot 2006]. Though it was already established that these CYP2C19 polymorphisms were more

[10] A "**Key Opinion Leader**" or "**KOL**" is an expert, typically a physician, with whom the drug companies work. Court's Exhibit F, at 66:08-66:19 [Gavin]. KOLs are individuals that give advice to the company and who speak on behalf of the company about a specific product. *Id.*

prevalent among certain Asian populations, Defendants took no action to update Plavix's label to inform prescribing physicians and patients about Plavix resistance.

39. That same month, during a Breakout Session of an Anti-Platelet Therapy Working Group, a group of Key Opinion Leaders told Defendants that they had their "head in the sand about . . . clinical resistance." P0082 at PLAV_JPP_BMS004481032 [2006 Anti-Platelet Therapy Working Group].

40. Throughout the first decade that Plavix was on the market, 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, and their past and present employees testified, that there were no available alternatives to Plavix for treatment of recent heart attacks. However, from even before Plavix's 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 they could not state or imply that Plavix was superior to aspirin or other antiplatelet medications because the scientific research did not support such a claim. P0115, P0116, P0125, P0127 [DDMAC Letters 1999, 2001, 2005, 2007]. For this reason, the FDA repeatedly told Defendants that such claims were, in the FDA's own words, misleading. P0115, P0116, P0125, P0127 [DDMAC Letters 1999, 2001, 2005, 2007]. 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. P0115, P0116, P0125, P0127 [DDMAC Letters, 1999, 2001, 2005, 2007]. 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.

41. Although the State has not asserted claims regarding Defendants' promotional materials for Plavix, these documents undermine Defendants' claims that Plavix was a wonder drug with no alternative courses of treatment. The FDA expressly said Plavix is not superior to aspirin. *See*, *e.g.*, P0115 at PLAV_SAN_01455747 [DDMAC Letter 1999] ("DDMAC stated that we considered this claim and similar claims to be misleading because . . . they imply superior efficacy of Plavix over aspirin, when such has not been demonstrated by substantial evidence"). As such, aspirin was an alternative that was just as effective as Plavix when they were used as monotherapy.

42. Over the years, despite Defendants' efforts to suppress studies about Plavix's diminished response, independent investigators began to develop a body of research regarding diminished response and its relation to CYP2C19, race, and clinical outcomes.

43. Beginning in 2006 and throughout 2007 and 2008, a number of important studies indicated that CYP2C19 polymorphisms were responsible for poor patient responsiveness to Plavix.[11] In late 2008, and continuing throughout 2009, additional studies established that

[11] *See* P0211 [Hulot, 2006] ("Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects."); P0314 [Brandt, 2006] ("Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel"); P0323 at [Giusti, 2007] ("Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients."); P0274 [Fontana, 2008] ("Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of cytochrome *P450* 2C19*2 allele on clopidogrel responsiveness").

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 responders.[12]

44. Defendants attempted at trial to show they were performing studies from 2006 and onward regarding resistance and CYP2C19. However, the State showed, and the Court finds, that none of these studies were adequately powered or designed to show any sort of link between Plavix resistance and clinical outcomes. Instead, Defendants designed studies or did retrospective analyses on study populations that would not endanger the safety profile of their drug. *See* P0030, at PLAV_PP_BMS00279638 [Local Studies Strategy Guide] ("trials that cannot be done . . . any study based on safety (clinical or biological) only"); P0584 at PLAV_PP_SAN00498959 [Clopidogrel Investigator-Initiated Trials – 2005 Guidelines and Strategies] ("No studies should be submitted that might jeopardize the current hypothesis and existing data on clopidogrel's mechanism of action...").

45. For example, the CHARISMA genetic sub-study was completed purportedly to examine whether CYP2C19 status affects outcomes. P0231 [Bhatt, 2012]. However, CHARISMA was a negative trial, meaning the underlying trial showed no benefit to users who took Plavix. Therefore, an analysis under CHARISMA was very unlikely to show any difference between CYP2C19 poor metabolizers and normal metabolizers. From even before the genetic

[12] *See* P0294 [Mega, 2008] ("Conclusion: Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had . . . a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers."); P0295 [Simon, 2009] ("Conclusion: Among patients with acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not.").

study was designed[13] to after the analysis was completed, employees and investigators recognized repeatedly that this study was not adequately powered to detect a correlation between poor metabolizers and outcomes.[14] Based on the above, the Court finds Defendants' attempt to present the CHARISMA genetic-sub study as evidence of a lack of correlation between CYP2C19 loss-of-function alleles and outcomes to be unpersuasive.

46. 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." P0294 at 354 [Mega, 2008] (emphasis added) (hereinafter "**Mega Study**"). The results of this study, in conjunction with the omeprazole issue, prompted the FDA to insist on the addition of language to the Plavix label explaining the CYP2C19 poor metabolizer phenomenon and noting the availability of genetic testing.

47. 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, 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,

[13] D2156 at –PLAV_BMS_00608077 [June 2006 Contact Report with Dr. Topol].

[14] P0726 at -PLAV_HIAG_SAN00247508 [2009 Analysis Plan for CHARISMA Genetic Substudy] ("[I]t would be inappropriate to extrapolate any potential absence of genotype effect found in this population to any population in which clopidogrel has a demonstrated benefit."); P0835 at PLAV_JPP_BMS00686475 [Stanton Email April 14, 2010].

> 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 [Hebden Email March 31, 2009] (Emphasis added).

48. The Court finds it significant that none of Defendants' Key Opinion Leaders regarding Plavix testified on Defendants' behalf at trial.

49. In May 2009, the FDA required Defendants to add information to the Plavix label regarding CYP2C19 and Plavix resistance. Court's Exhibit C, at 155:15-208:14 [Hebden]; *see also* P0535 [Hebden Email December 2008]; P0536 [Medical Review Group Chair Meeting notes]; P0540 [Response Letter to FDA Strategic Decision Discussions March 2009]; P0541 [Additional Draft of Response Letter March 2009]; P0410 [May 2009 Plavix Label].

50. 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 black box warning, and to move information regarding this issue to the Warnings and Precautions section of the label. Court's Exhibit J, at 428:25-429:15 [Emison]; *see also* P0411 [March 2010 Plavix Label].

51. Defendants asserted that a November 2009 label included warning information before the 2010 black box warning was mandated. However, Dr. Plunkett testified, and the Court finds, that consistent with all the documents in this case, there is no evidence the November 2009 label referenced by Defendants in their questioning was ever published to patients or doctors.

52. Under FDA regulations, a boxed warning is a section of the drug label reserved for serious warnings, particularly regarding risks that may lead to death or serious injury. 21 CFR 201.57(c)(1).

53. The 2010 boxed warning stated the following:

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

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)]*.

P0411 [March 2010 Plavix Label] (Emphasis in original).

54. 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.

D2107 [September 2016 Plavix Label] (Emphasis in original).

55. Defendants argued, and their former and present employees testified 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 Court finds that Defendants knew of the risks associated with Plavix resistance from before the drug was launched and, as such, this information triggered Defendants' duty to provide a warning that adequately described those risks as soon as they became apparent, regardless of whether they had

discovered the cause of this risk. Defendants did not offer any credible evidence to challenge the existence of this duty.

56. Defendants also argued repeatedly, and their former and present employees testified at 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 Plavix resistance. Defendants and their former and present employees argued and testified they could not possibly have determined whether people with CYP2C19 polymorphisms experienced diminished effectiveness from the drug. The Court is not persuaded by Defendants' arguments and this testimony. The State's allegations and evidence was not restricted to CYP2C19. As was shown in this retrial, Defendants knew of the risk that Plavix would be less effective or ineffective for a substantial percentage of the patient population. The facts presented at trial show, and the Court finds, that Defendants knew about the risk of diminished response and had the ability to update the Plavix label continuing from launch until many years after. Yet, Defendants did not update the label and instead chose to establish a policy of inaction and denial.

57. Indeed, Dr. Roome testified that the issue of genetic polymorphisms of the CYP enzymes was on Defendants' radar even prior to launch of Plavix. As such, the Court finds that Defendants, as of 1998, had sufficient knowledge to trigger their duty to update the Plavix label to warn about the risk of variability of response, particularly with regard to patients with genetic mutations of CYP2C19, but nevertheless omitted such information.

58. Defendants and their past and present employees argued at trial that, because the 2016 boxed warning deleted any reference to a causal relationship between CYP2C19 poor metabolizer status and clinical outcomes, the FDA no longer considers the poor response issue to be important. The Court finds that argument unpersuasive. Because boxed warnings are

reserved only for the most serious risks of injury or death, and the boxed warning appears on the Plavix label to this day, clearly the FDA continues to consider reduced effectiveness of Plavix to present a serious risk of injury or death. Further, the Court is instead persuaded by the evidence, as shown in the 2022 update to the Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy document, which says the 2016 label update broadened the warning to all patients and not just subsets of patients with ACS or those undergoing PCI. P0771 at 961 [Lee, 2022].

59. Moreover, to this day, Defendants directly tell patients in the Medication Guide that, if they are poor responders, the drug may not work as well for them. P0833 [2022 Plavix Label]. The Court finds that when this is said in the context of a medication that is intended to lower the risk of a heart attack or stroke, the only reasonable interpretation of the message that Plavix "may not work as well for you" is that Plavix may not lower the risk of a heart attack or stroke for poor metabolizers. Dr. Roome agreed during her testimony that this phrase means that poor metabolizers may not be protected. The Court so finds.

60. Dr. Roome testified, and the Court finds, that it is quite important for prescribing doctors and patients to be fully informed as to the relevant scientific and medical information about a drug every time a prescription is filled and refilled. That information is needed so the patient, in consultation with his or her physician, can receive the best care and make an informed decision as to whether to take a particular drug. That important information, according to Dr. Roome, should be on a drug label. The Court agrees and so finds.

61. Applying an objective standard, the Court finds that a consumer acting reasonably under the circumstances would find information regarding diminished response of this drug

important to their choices in deciding what treatment to undergo, as the evidence showed during trial.

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

63. 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 his prolific research, Dr. Gurbel remains a practicing clinical cardiologist, cardiac interventionalist, and leading expert on Plavix. *See* P0358 [Curriculum Vitae of Dr. Paul A. Gurbel].

64. 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.

65. 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.* P0358 [Curriculum Vitae of Dr. Paul A. Gurbel].

66. Since shortly after Plavix was first introduced to the market, Dr. Gurbel's research has paved the way in understanding Plavix's effects. His laboratory pioneered the concept of antiplatelet response variability, a major weakness of clopidogrel. Dr. Roome, a senior medical employee at Sanofi who testified at trial and who was intimately involved with Plavix over the years, readily agreed she has referred to Dr. Gurbel as an important and brilliant Key Opinion Leader, and the world-wide specialist in Variability of Response.

67. At trial, Dr. Gurbel explained why he focused so much of his research on Plavix, testifying that thrombosis in coronary arteries is what kills patients. Even if a patient develops a clot and ultimately dies from ventricular fibrillation, the primary event that closes the artery is aggregation of platelets. In other words, it is the clot that kills the patient. Thus, Plavix, which is designed to prevent those clots, has to work all the time in order to prevent catastrophe.

68. Dr. Gurbel further elaborated, and the Court finds, that because doctors were relying on this workhorse drug to prevent fatal events, it was exceedingly important that doctors understand Plavix's limitations, and that everyone else involved in the care of the patients (and the patients themselves), be informed. Patients receiving a stent or getting bypass surgery to prevent catastrophe needed to know whether they could truly rely on the drug to work all the time and as expected.

69. Dr. Gurbel first expressed concern to Defendants about the lack of platelet inhibition in some patients around the year 2000.

70. Although Defendants' past and present employees testified that Defendants conducted many studies into resistance, the Court finds (as Dr. Gurbel testified) that Defendants did no meaningful research in this area, and sponsored no studies on Plavix resistance, its causes, or its clinical implications. On this point, Dr. Gurbel systematically addressed the individual

studies which Defendants argued reflected meaningful efforts on their part to investigate Plavix resistance. In the Court's view, Dr. Gurbel thoroughly refuted Defendants' argument that they engaged in any efforts to study resistance.

71. Responding to defense arguments that a study of 45,000 Chinese patients in a clinical trial known by the acronym "**COMMIT**" demonstrated Plavix works just as well for East Asians as for other races, Dr. Gurbel established that the risk reduction seen in the Chinese patients in COMMIT was less than half of the risk reduction seen in Caucasian patients in the CURE study. Thus, the COMMIT study actually demonstrated that Plavix was *less* efficacious for Chinese patients—where rates of CYPC2C19 loss of function alleles are high—as compared to the risk reduction seen in Caucasians.

72. Responding to Defendants' contention that Defendants could not conduct studies that would establish a link between CYP2C19 poor metabolizers earlier than 2008, Dr. Gurbel established that there were, in fact, no technological limitations to them performing such a study. All of the tools (including genetic tests to identify CYP2C19 poor responders) and background knowledge necessary to conduct a simple study in this area were available to Defendants prior to the launch of Plavix.

73. Dr. Gurbel and his colleagues were only able to conduct smaller studies, despite enormous interest in the area of Plavix resistance, because Defendants refused to fund them or supply the drugs needed for larger studies. To put together a large-scale trial, such as a study in the tens of thousands (which was needed to develop the necessary data), a large amount of funding is needed. That funding typically comes from a drug manufacturer. But drug manufacturers are averse to funding studies that might cut into their market share, i.e., total sales of the drug. As a result, such large-scale studies are rarely conducted.

74. Dr. Gurbel additionally explained the necessity of knowing the information related to Plavix resistance in the 1998 through 2010 time frame. Stenting a patient can result in serious harm, in the form of stent thrombosis, if there is not an antiplatelet drug protecting the patient from clotting. If cardiologists knew that a significant portion of patients taking Plavix would get an insufficient benefit from the drug, they would pursue alternative courses of treatment (e.g., coronary artery bypass surgery, the use of different anti-clotting drugs, increased monitoring, doubling the dose of Plavix, etc.). Because procedures like stenting were so new in the early 2000s, doctors began performing them regularly because they were told Plavix was protecting their patients. Many people died after those procedures due to stent thrombosis. Had doctors known about the severe limitations of Plavix, many of those deaths may have been avoided.

75. The Court finds Dr. Gurbel's testimony credible and highly persuasive.

76. The State also offered the testimony of pharmacology, toxicology and prescription drug regulation expert Dr. Plunkett at trial.

77. Dr. Plunkett is a pharmacologist, toxicologist, and an 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. P0357 [Curriculum Vitae of Dr. Laura M. Plunkett].

78. 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. She has specific expertise in cardiovascular pharmacology, which is the study of drugs used to treat cardiovascular diseases, including antithrombotic drugs. She also has 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. P0357 [Curriculum Vitae of Dr. Laura M. Plunkett].

79. As a result of her training and work with various clients, Dr. Plunkett has knowledge, experience, and expertise related to changes in FDA regulations. She is highly published including peer reviewed literature and book chapters about pharmacovigilance. She works regularly as a consultant for pharmaceutical companies submitting drug applications and labels. 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. P0357 [Curriculum Vitae of Dr. Laura M. Plunkett].

80. Dr. Plunkett testified and the Court finds that Defendants were obligated[15] to update their label to include a warning that a significant portion of the population experiences a diminished response to Plavix. Her opinion that the label should be updated and further studies were required to be done is based upon 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, and the signal Defendants identified in their CAPRIE trial that identified a significant interaction between treatment and race.

[15] As evidenced by the federal regulations and Dr. Plunkett's experience in working with drug companies on labeling issues.

81. Dr. Plunkett also testified and the Court finds that, in practice and 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. It is appropriate for a pharmaceutical company to update its label when there is a reasonable basis to believe that there is a causal association with a risk.

82. Addressing Defendants' contention that they had no duty to investigate the reasons for the diminished response to Plavix reflected in the 1998 Meta-Analysis and other available information, Dr. Plunkett testified, and the Court finds, that drug companies like Defendants have an obligation to investigate potential problems with their drugs. A drug manufacturer's basic obligation includes pharmacovigilance and post-market surveillance and otherwise includes continual analysis of data once the drug is approved. In the paradigm for drug development and approval, the manufacturer knows it is testing the drug in a selective population for the purposes of the clinical study that may or may not be relevant to the real-world experience of patients. As a result, drug companies must perform post-market surveillance of their drugs, as well as keep up-to-date with the current medical literature, in order to understand whether their drugs exhibit risks in the real world that are different in kind, frequency, or severity from those that were detected during their clinical development, or to determine if benefits seen in the clinical setting are less evident or are absent in a real-world setting.

83. Like Dr. Gurbel, Dr. Plunkett testified about the importance of drug companies providing funding for clinical trials. Drug companies have the resources to provide the drug to investigators and the manufacturer is the single best source of knowledge about the drug. Because large clinical studies can be very expensive, it is often difficult for researchers to secure

the necessary funding for such trials. As a result, it is the drug manufacturer's responsibility to cooperate with outside investigators who seek to conduct studies about the manufacturer's drugs.

84. As Dr. Plunkett testified, the Court finds that prior to addition of the boxed warning, neither Defendants nor anyone else conducted any large clinical trials relating to the poor metabolizer issue which had sufficient power to definitively answer questions related to Plavix resistance and poor responders. Specifically for individuals who carry two loss-of-function alleles, Defendants did not do sufficient research to investigate that issue, even though they had known about an increased risk for such individuals since before launch of the drug.

85. The Court finds Dr. Plunkett's testimony credible and persuasive.

86. Defendants knew at the time of launch of Plavix in December 1998 that there was a significant risk associated with diminished patient response to Plavix, particularly in members of non-Caucasian races. For many years after the launch of Plavix, Defendants deliberately turned a blind eye toward the diminished response problem because of Defendants' concern that addressing that problem might adversely affect Plavix sales and Defendants' profits. Defendants deliberately withheld information from the FDA and the greater medical community about the risk. Defendants engaged in a pattern and practice of rejecting any proposed studies that might call attention to or generate interest in the risk associated with Plavix resistance. Defendants failed to conduct any studies that were designed and adequately powered to investigate Plavix resistance and/or the impact of race and/or CYP2C19 polymorphisms on inhibition of platelet response in Plavix patients. By engaging in the foregoing conduct Defendants intentionally set back the progress of research into the risks associated with Plavix resistance by many years. By doing so, Defendants knowingly placed Plavix patients at grave risk of serious injury or death in order to substantially increase their profits.

87. Following FDA approval but prior to Plavix's launch, Defendants knew the risks of diminished response to Plavix exhibited by a substantial percentage of patients such that Defendants could have changed Plavix's label under the FDA's Changes Being Effected regulation ("**CBE**") to warn patients and physicians about that risk. Defendants did not update their drug label to inform consumers of the risks of Plavix resistance. The label did not adequately warn about the diminished response risk until March 2010.

88. After the black box warning was added to the label in 2010, Plavix sales declined. According to Defendant BMS's employee and Rule 30(b)(6) designee, Brian Goodman, from shortly after the black box warning was imposed, sales of Plavix in Hawai'i declined 20% over the next two years. Court's Exhibit K, at 231:15-233:08 [Goodman]; P0785-P0789 [BMS 10-Q Filings Oct. 2008-Apr. 2012]. This testimony was corroborated by the State's expert Dr. Nicole Maestas. Defendants' one corporate representative, Dr. Roome, as well as internal contemporaneous corporate documents, also point to the black box warning as causing an immediate and substantial drop in sales. At the end of the two-year period after the black box warning was added, Defendants' exclusive patent on Plavix expired and for all practical purposes sales of brand-name Plavix dropped to extremely low levels. P0344 [Plavix Prescriptions Chart, 2007-2012] (showing steep decline when generic is launched in 2012). Plavix sales did not return to pre-boxed warning levels.

89. BMS's 10-Q documents filed with the SEC also show that sales declined following the addition of the black box warning. P0785-89 [BMS 10-Q Filings Oct. 2008-Apr. 2012]. Before the black box warning, Plavix sales were increasing every year. *Id.* But after the black box warning, Plavix sales across the United States declined for the remaining years of exclusivity. *Id.* The State's expert, Dr. Maestas, confirmed these trends in her analysis of

prescription sales data for Plavix: in the years prior to the black box warning, Plavix sales were increasing annually; yet, from the month the black box warning was added, Plavix sales declined and had a negative trend every year for the remaining years of exclusivity. Defendants' internal documents reflect their acknowledgment that even a 1% drop in sales would have a large impact on revenue derived from Plavix. P0804 [Feldman Email March 7, 2011] ("Subject: Plavix Timeline of Events"). Here, the evidence showed a 20% drop within the State of Hawai'i.

90. Defendants argued and their past and present employees testified that the drop in sales could be attributed to any number of factors, including the natural lifecycle of a prescription drug. The Court rejects this for several reasons. First, Defendants' own witness, Dr. Roome, admitted at trial that she was aware that sales of Plavix dropped because of the black box warning. Second, Defendants' internal documents showed that in analyzing Plavix sales before and after the black box warning they did not believe Plavix would follow any sort of natural lifecycle of a drug. P0802 at PLAV_JPP_BMS01936309 [PowerPoint – World Review MAT 2010 Q1]. Before the black box warning was added, Defendants themselves expected Plavix sales to continue to increase until exclusivity was lost. *Id.* Moreover, an internal document from Defendants discussed the black box warning as one of the causes of the major decline in sales. P0804 [Feldman Email March 7, 2011] ("Subject: Plavix Timeline of Events"). Nothing in that document discussed the natural lifecycle or declining marketing of the drug in the years leading up to loss of exclusivity. *Id.*

91. The black box warning also caused a shift in the cardiology community once the issue of diminished response was finally warned about. A few months after the addition of the black box warning, the American College of Cardiology ("**ACC**") and the American Heart Association ("**AHA**") issued a Clinical Alert regarding the black box warning and updated their

practice guidelines to recommend that prescribing physicians consider genetic testing for high-risk patients.[16] P0106 [2010 ACCF/AHA Clopidogrel Clinical Alert]. These guidelines recommended that doctors consider changing the antiplatelet drug used if the patient is found to be a poor metabolizer. *Id.* Several leading medical institutions changed their treatment policies to include genetic testing for CYP2C19 poor metabolizers before starting treatment with Plavix, and health insurers began reimbursing for genetic testing of Plavix patients for CYP2C19 polymorphisms. P0793 [Hughes, 2010]; P0797 [Label Change Market Intelligence Summary slide deck]; P0773 at 18 [Empey, 2018]. The State also presented evidence that at least one Hawai‘i cardiologist—described as a thought leader by Defendants—began testing all his Asian patients on Plavix for CYP2C19. P0803 at PLAV_JPP_BMS02824318 [2010 BMS Field Medical Science Update PowerPoint]. The fact that these medical organizations and institutions changed their policies, and the cardiology guidelines incorporated the recommendations as they related to testing for non-functional alleles, shows the importance of this information to patient treatment. While the importance of information as determined by doctors is not synonymous with information considered important by consumers, the evidence shows that once the information was disclosed to the medical community, it was regarded as having clinical importance when treating patients. In the 2010 Clinical Alert that was issued, the ACC and AHA stated ". . . both clinicians and patients need to be aware of genetic polymorphisms that may modulate clopidogrel responsiveness and cause MACE [major adverse cardiac events]." P0106 [2010 ACCF/AHA Clopidogrel Clinical Alert].

[16] Defendants argued that the 2021 Guidelines removed the recommendations regarding testing and Plavix poor response. However, the evidence and testimony did not support this argument.

92. At trial, Defendants presented two Hawai‘i cardiologists. Dr. Todd Seto practices general cardiology and Dr. John Kao practices interventional cardiology. They both testified that the information in the black box warning did not change their practices, and that they did not find the diminished response information important to their practice. Further, these cardiologists testified that they knew of no Hawai‘i cardiologists who were testing their patients for CYP2C19 loss-of-function alleles. The Court did not find their testimony to be persuasive.

93. In essence, these experts testified that they did not give any weight or credence to the black box warning because they felt it did not provide them with relevant information or tell them what to do about the information it did provide. They testified instead that they rely upon the practice guidelines of their professional medical organizations, the ACC and/or AHA, to tell them what to do. These witnesses testified that they follow their professional guidelines instead of the black box warning. However, the evidence showed that Defendants' witnesses were not actually following the ACC/AHA guidelines and/or were misstating what the guidelines recommended or required, or both. For example, the ACC/AHA guidelines encourage physicians to engage in shared decision-making with their patients and to take into consideration and respect the patient's preferences regarding treatment. D1232 at e578 [2011 ACCF/AHA/SCAI PCI Guidelines]. The witnesses testified that they agree with these principles. But they then also testified that they prescribe Plavix to most of their patients and do so without ever discussing the boxed warning with any of them. They also testified that they never genetically test any of their Plavix patients to determine whether they may be poor responders, without ever discussing with their patients the availability of genetic testing or asking the patients whether the patients would like to undergo genetic testing.

94. Dr. Kao and Dr. Seto sought to justify their actions by asserting that the ACC/AHA guidelines recommend against routine genetic testing. But *routine* genetic testing has never been an issue in this case. In truth, the guidelines do not prohibit genetic testing and indeed include a Class IIb recommendation that doctors may consider genetic testing for high-risk patients. D1232 at e615-616 [2011 ACCF/AHA/SCAI PCI Guidelines]. But rather than considering genetic tests for his patients, Dr. Seto actively discourages other cardiologists from using testing. In fact, however, the guidelines say that a Class IIb recommendation means that the benefit is greater than or equal to the risk for that method of treatment, despite the fact that, in the ACC/AHA's view, the usefulness or effectiveness of the treatment is unknown, unclear, uncertain, or not well established. Defendants repeatedly argued that the guidelines never recommended genetic testing. However, the plain language of the IIb recommendation demonstrates that genetic testing is in fact a recommendation in the guidelines.

95. Based on the totality of the evidence presented at trial, the Court gives little weight to the testimony of either Dr. Seto or Dr. Kao on many critical factual issues.

96. Regardless of these doctors' stated positions on the information regarding diminished response, the Court finds that the information regarding diminished response is something that would be material to a reasonable consumer. When the Court buttonholed Dr. Kao about the importance of a test result showing two non-functional alleles, and asked Dr. Kao whether he would speak with his patients about such a test result, Dr. Kao stated that he would, in fact, discuss the significance of the test result with the patient. This demonstrates that even Defendants' witness recognized that the information about diminished response is something a patient needs to know when making his or her treatment decisions.

97. In addition, Defendants themselves conducted a survey of physicians they targeted, including cardiologists in the US for the express purpose "to understand how physicians would react to the new label, as well as assess how this could impact Plavix usage." P0104, at PLAV_JPP_SAN00825678 [Physician Response to Plavix Label Change, April 2010]. The survey showed that numerous cardiologists did, in fact, find the information in the black box warning to be important to their practice. *See*, *generally*, P0104. Defendants' survey, introduced by the State, showed (a) that the label change opened the door to cardiologists using alternative drugs for current patients experiencing problems with Plavix, and potentially for all high-risk ACS patients (*Id*. at PLAV_JPP_SAN00825687); (b) that most physicians surveyed said a positive genetic test would lead them to immediately switch to another drug to avoid the risk of a negative outcome (*Id*. at -689);(c) that most neurologists who participated in the study said the label change lowers the threshold to switch to another drug, like Aggrenox, when a patient has a recurrent event on Plavix (*Id*. at -711); and (d) that most cardiologists surveyed said they would switch to another drug whenever a patient has a recurrent event or symptoms since the patient is likely a poor metabolizer. *Id*. at -712.

98. Defendants presented evidence that insurance companies and the State's Medicaid programs continue to allow doctors to prescribe Plavix and did not place any restrictions or pre-conditions on them doing so after the black box warning was added. Defendants argue that this means the State did not consider the black box warning important, because, as Defendants theorized, if the State did consider the information important, it would have issued protocols restricting Plavix or imposing pre-conditions on its use, such as prior authorizations or mandatory genetic testing. The Court does not find this argument, or the evidence underlying it, persuasive. The responsibility to ensure that patients and physicians are aware of the limitations

of a drug rests squarely with the manufacturer, *Wyeth v. Levine*, 555 U.S. 555, 579 (2009), not with the State's Medicaid system. As such, the State's decision to not place restrictions on Plavix has little probative value as to whether the information was important to consumers.

99. The State's claims in this case are that Defendants failed to warn about safety and efficacy information in their label. At no point in the trial did the State argue that Plavix should be restricted or that it is unsafe. The Court has no doubt whatsoever that Plavix has been and can be a critically important and useful drug to many patients, but Defendants should have warned about the serious limitations of Plavix for certain patients so that patients and physicians could coordinate to make informed decisions for patients care. The evidence regarding the State of Hawaii's Medicaid programs and other insurance programs, which leaves the decision as to the course of treatment up to the doctor (and the patient) (Court's Exhibit O, at 35:18-45:05 [Lopez]), is not inconsistent with the State's position and therefore has little if any probative value.

100. Defendants also argued that the CYP2C19 issue and Plavix resistance was not a real problem for patients. However, the evidence presented at trial proved otherwise. First, the FDA still requires the Plavix label to include a black box warning and a Medication Guide about diminished response to Plavix. Notably, the Plavix drug label was updated in September of 2022. P0833 [September 2022 Plavix Label]. If, as Defendants' experts testified, current science proves there is no risk associated with resistance to the drug, Defendants and/or the FDA would have removed the boxed warning from the label. The September 2022 label evidences that Defendants' assertions to the Court are inconsistent with the assertions they have been making and continue to make to patients for the last 13 years. Defendants argued to the Court there is no problem with the drug, but a Hawai‘i consumer who fills a Plavix prescription on the date of this

Order is still told by Defendants that the fact Plavix might not work as well in people with certain genetic factors is the most important information they need to know.

101. Overall, the Court finds that Plaintiff offered substantial evidence regarding the materiality of the risk of diminished response to patients and physicians—including, but not limited to, the steady decline in sales that totaled a 20% drop in Hawai‘i, the substantial number of doctors and medical institutions that changed their practices and guidelines in response to the black box warning, the fact that the FDA found this information important enough to be added to a black box warning, and the fact that Defendants' Medication Guide says to this day that the fact that Plavix may not work as well for certain people is the most important information a patient needs to know. The testimony of Defendants' experts, conflicting at times with their own guidelines, and exhibiting practices that seem to give no weight to their patients' right to shared decision making, is ultimately unpersuasive.

102. The Court also finds that there was evidence of harm to Hawai‘i consumers as a result of Defendants' conduct. Coronary heart disease is the number one killer of both men and women in Hawai‘i, as testified by Dr. Seto. Defendants' medical experts testified that the racial makeup of their patients has been roughly equivalent to that of the population of the state as a whole. Dr. Seto testified that 70% of his patients are of East Asian or Pacific Islander descent. The issues raised by this lawsuit are clearly of major significance to the people of Hawai‘i.

103. The studies presented at trial showed that Asians and Pacific Islanders have a particularly high percentage of CYP2C19 poor responders (P0697 [Ionova, 2022]; D1946 [Koo, 2021]), but that persons of all races are at risk, to a greater or lesser degree, of being a CYP2C19 poor responder. *Id.*

104. At trial, Defendants argued that the percentage of variability accounted for by CYP2C19 loss of function alleles was extremely low, only 12%. However, Dr. Gurbel testified, and the Court finds, that it doesn't matter if it's 12 percent or 4 percent or 8 percent. It's enough of a contribution to be associated with a tripling or quadrupling of the risk of stent thrombosis.

105. Plavix resistance affects approximately one third of the population nationwide.[17] Additionally, those people who exhibit Plavix resistance have been repeatedly shown to be at an increased risk of clinical outcomes when viewed by the weight of the evidence.[18] Loss of function allele carriage status similarly has been definitively linked to an increased risk of MACE and cardiovascular death.[19]

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[17] *See e.g.,* P0037 at 92 [1998 Meta-Analysis]; P0259 [Järemo, 2002]; P0255 [Gurbel, 2003]; P0262 [Mobley, 2004]; P0263 [Angiolilo, 2004]; P0238 at 5 (Table 2) [Gurbel, 2006]; P0721 [Michelson, 2019] at 941("A significant proportion of subjects (about 1/3) treated with clopidogrel are very poor responders, displaying almost no inhibition of platelet function."); *Id.* at 998 ("A fourth paradigmatic shift arose with the recognition that 30%-40% of individuals receiving clopidogrel were functionally nonresponsive.").

[18] *See e.g.,* P0292 [Matetzky, 2004]; D1158 [Gurbel, 2005]; P0250 at 926-7 (Table 1); [Bonello, 2010]; P0666 [Brar, 2011]; D1157 [Gurbel, 2012]; P0677 [Cavallari, 2018]; P0715 at 1522 [Sibbing, 2019] ("[A] multitude of studies have consistently shown that PCI-treated patients with impaired clopidogrel-induced platelet inhibition to be at an increased risk for ischemic events, in particular stent thrombosis."); P0721 at 661 [Michelson, 2019] ("The clinical implications of an inadequate response to clopidogrel therapy have been evaluated by a large number of studies. HRPR ADP by all established platelet function tests has been associated with the occurrence of adverse ischemic events in different patient populations, in particular in patients undergoing PCI."); *Id.* at 991 ("Antiplatelet nonresponsiveness was brought forefront when data suggesting insufficient DAPT increased risk of stent thrombosis nearly 100-fold.")

[19] *See e.g.,* P0294 [Mega, 2008] ("Conclusion: Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had . . . a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers."); P0295 [Simon, 2009] ("Conclusion: Among patients with acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not."); P0709 at 615 [2011 ACC/AHA Guidelines on PCI] ("Patients with decreased *CYP2C19* function because of genetic polymorphisms metabolize clopidogrel poorly

106. Based upon the various studies discussed at trial and/or otherwise introduced into evidence, the weight of the evidence is that approximately one-third of the overall population are carriers of CYP2C19 loss-of-function alleles. Given that Asians and Pacific Islanders have generally been found to have considerably higher rates of CYP2C19 loss-of-function alleles than other races, coupled with the fact that Asians and Pacific Islanders make up a much larger percentage of the Hawai‘i population (D2491 [State of Hawai‘i Data Book 2010]) than would ordinarily be found almost anywhere else in the United States, the Court finds that the percentage of the population in Hawai'i who are carriers of the CYP2C19 loss-of-function alleles is higher than that overall average in the nation.

107. The Court also finds, based on the totality of the evidence, that a significant number of Plavix patients in Hawai‘i were unnecessarily exposed to the risk of an adverse event, including serious physical injury or death, because they were carriers of CYP2C19 loss-of-

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and have higher rates of cardiovascular events after ACS and PCI than patients with normal *CYP2C19* function."); P0715 at 1533 [Sibbing, 2019] (Taking the available evidence into consideration, strong and consistent associations were observed for CYP2C19 LoF (*2 and *3) alleles with ischemic events including stent thrombosis . . ."); P0721 at 667 [Michelson, 2019] ("Loss-of-function polymorphisms of the CYP P-450 enzyme system impair hepatic metabolism of clopidogrel to its active form resulting in HRPR ADP and an increased risk of MACE during clopidogrel therapy. In particular, carriers of the *2 allelic variant of CYP2C19 were more likely to exhibit a poor response to clopidogrel and develop ischemic risk."); *Id.* at 998 ("Moreover, high on-treatment platelet reactivity and slow metabolism (e.g. carriers of CYP2C19 *2 allele) correlate with ischemic risk while low on-treatment reactivity and fast metabolism (e.g. CYP2C19 *17) correlate with bleeding."); P0682 [Wang, 2021] ("Among Chinese patients with minor ischemic stroke or TIA who were carriers of *CYP2C19* loss-of-function alleles, the risk of stroke at 90 days was modestly lower with ticagrelor than with clopidogrel."); P0681 [Pereira, 2021]; P0771 at 961 [Lee, 2022] ("[S]ubstantial evidence exists linking *CYP2C19* no function alleles with poorer clinical outcomes among patients with clopidogrel-treated ACS, particularly those undergoing PCI, likely as a result of decreased clopidogrel active metabolite formation."); P0772 at 830 [Lee, 2023] ("The *CYP2C19* gene has polymorphisms, and its loss-of-function allele is associated with the poor metabolism of clopidogrel, followed by an increased risk of cardiovascular events.").

function alleles. The State presented sufficient evidence to show that there were alternative courses of treatment that could have been taken had patients and physicians been informed of the limitations of Plavix. Therefore, by depriving consumers of the diminished response information, Defendants denied Hawai‘i consumers the ability to make an informed decision regarding their care, which based on the evidence presented at trial is inconsistent with the national guidelines Defendants' medical experts purport to follow. Based on the weight of the evidence presented at trial, the statistical likelihood that every CYP2C19 poor or intermediate responder in Hawai‘i escaped unscathed from Defendants' failure to disclose the poor responder issue and the availability of genetic testing is, in the Court's view, not only highly improbable, but not reasonably possible.

108. The Court's finding is supported by the testimony of the State's interventional cardiology expert, Dr. Gurbel, who testified that Hawai‘i patients *did* suffer physical harm as a result of Defendants' nondisclosure and concealment.[20]

109. Moreover, common sense and ordinary life experience tell us that, for every consumer-patient who was injured by Defendants' misconduct, and in most circumstances many others around them—friends, family and other loved ones—also suffered as a result.

110. The Court finds that Hawai‘i consumers were injured as a result of Defendants' omissions from the Plavix drug label. Withholding such important and vital information regarding whether a preventative cardiovascular drug works can quite literally mean the difference between life and death. The fact that Hawai‘i consumers were prevented from learning

[20] Dr. Seto also testified that he had patients die of recurrent ischemic events while on Plavix. However, he could not say whether those patients died as a result of being poor metabolizers because he never tests his patients for loss of function alleles or reduced platelet inhibition.

this information due to Defendants' failures to update the label and their suppression of studies surrounding CYP2C19 poor responders and Plavix resistance in general constitutes injury.

111. At trial, the State presented the expert testimony of Dr. Maestas regarding the number of retail prescriptions, refills and non-retail units sold in Hawai‘i between December 1998 and March 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.

112. Dr. Maestas calculated the number of retail prescriptions, refills and non-retail units sold during the relevant time period to be 834,012. P0349 [Maestas table 3.c., summarizing results].

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

114. Defendants' unfair conduct, as affirmed on appeal, continued for a period of approximately 4,100 days, from December 1998 through March 12, 2010.

115. 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

1. This Court has jurisdiction over the parties and the claims in this action.

2. 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

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

4. 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.*

5. 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." *Shikada*, 152 Hawai'i at 443, 526 P.3d at 420.

A. Deceptive Acts or Practices of Defendants

6. Based on the totality of the evidence discussed above, including the nature of the conditions involved, the potential severity of the risks involved, and the potential and likely consequences if a poor responder unwittingly relied on Plavix to protect himself or herself; and taking into account the credibility of the witnesses and the content and character of the

documentary evidence, the Court concludes that Defendants' omissions from the Plavix label were deceptive under UDAP.

7. A practice is deceptive within the meaning of UDAP when (1) there is a representation, omission, or practice (2) that is likely to mislead consumers acting reasonably under the circumstances and (3) the representation, omission, or practice is material. *Shikada, supra*, 152 Hawai'i at 443, 526 P.3d at 420 (citing *Courbat v. Dahana Ranch, Inc.*, 111 Hawai'i 254, 262, 141 P.3d 427, 435 (2006)).

8. The Hawai'i courts have made it clear that a material statement or omission is "deceptive" if it had "the capacity or tendency to mislead or deceive[.]" *Courbat v. Dahana Ranch, Inc.*, 111 Hawai'i 254, 261, 141 P.3d 427, 434 (2006), quoting *State ex rel. Bronster v. United States Steel Corp.*, 82 Haw. 32, 50, 919 P.2d 294, 312 (1996) (emphasis added).

9. UDAP does not require a plaintiff to show that there was any actual deception, nor that the defendant had an intent to deceive. *Courbat*, 111 Hawai'i at 262 n.9, 141 P.3d at 435 n.9.

10. The Supreme Court of Hawai'i has stated that, "Under UDAP, a representation or omission is considered material if it involves information that is important to consumers and, hence, likely to affect their choice of, or conduct regarding, a product." *Shikada, supra,* at 440, 526 P.3d at 417 (quoting *Courbat*, 111 Hawai'i at 262, 141 P.3d at 435) (internal quotations omitted; emphasis added). This test "is objective, not subjective" and "considers the viewpoint of the 'reasonable consumer, not the particular consumer.'" *Id.*

11. There is a rebuttable presumption of materiality for "claims that significantly involve health, safety, or other areas with which the reasonable consumer would be concerned, including a claim that concerns the purpose, safety, efficacy, . . . performance, . . . or a finding by

another agency regarding the product." *Novartis Corp. v. FTC*, 223 F.3d 783, 786 (D.C. Cir. 2000) (construing the Federal Trade Commission Act "**FTC Act**"); *see also Tokuhisa v. Cutter Mgmt. Co.*, 122 Hawai'i 181, 195, 223 P.3d 246, 260 (App. 2009) (finding that Hawai'i courts should look to federal cases interpreting the FTC Act when interpreting Hawaii's UDAP statutes).

12. However, the Supreme Court has observed that "[o]vercoming the presumption is 'not a high hurdle." *Shikada*, 152 Hawai'i at 441, 526 P.3d at 418. It "does not end things" and is "not 'an inflexible rule that eliminates [the] need to look at materiality on a case-by-case basis.'" *Id.*

13. As the Supreme Court found, pharmaceutical companies have a common law duty to warn consumers "when risks of a particular drug become apparent." *Shikada*, 152 Hawai'i at 444, 526 P.3d at 395 (quotation omitted). The Court acknowledges that 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 FDA's CBE regulation. *See* 21 C.F.R. § 314.70(c)(6)(iii)(A); *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019).

14. The Court concludes that Defendants knew enough about the poor responder issue after FDA approval but prior to launch to trigger a duty under state law to update the Plavix label to warn patients and physicians about the risks associated with lack of response or diminished response, and that, given the FDA's expansive definition of "newly acquired information," to effectuate that update through the CBE regulations.[21] Defendants had sufficient knowledge, as

[21] The definition of "**newly acquired information**" provided in 21 CFR § 314.3(b) is: Newly acquired information is data, analyses, or other information not previously submitted to the

well as the technical ability, to investigate the cause of Plavix resistance, which was known to Defendants before the drug launched in December of 1998.

15. The Court also concludes that the safety and efficacy information omitted from the Plavix label was material to consumers. The State has presented substantial evidence to show that, applying an objective standard, consumers acting reasonably under the circumstances would find the information omitted from the Plavix label to be important and would likely affect their choice or conduct regarding whether to use Plavix. Common sense also leads to the inevitable conclusion that the omitted information is material to a reasonable person faced with the medical issues for which Plavix can be prescribed. The most relevant period for examining materiality is the time from the launch of Plavix in December 1998 until the black box warning was first used in March 2010. That is the time period put at issue by the State. Therefore, that is the time period when materiality must be determined, based upon the state of medical knowledge and other pertinent circumstances at that time. Even without the presumption of materiality for health and safety information, the above discussed findings of fact are sufficient to demonstrate materiality. The State has therefore met its burden to show materiality.

16. The Court also concludes that the omission of this material information had the tendency or capacity to mislead consumers. The ability to give informed consent to medical treatment is a well-established tenet of our jurisprudence. It was important that the most up-to-date medical and scientific information was on a label so that prescribing physicians could give the best treatment or care to the informed patient. As established at trial, doctors are expected to

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Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analysis of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

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 like Plavix, which is intended to lower the risk of heart attacks and strokes, certainly has the capacity and likelihood to mislead reasonable consumers. Given that drug manufacturers have a duty to disclose known safety risks and update label information under Hawai‘i law, the Court concludes that Defendants' omission of the risks of diminished response to Plavix had the tendency or capacity to mislead consumers into believing that no such risk existed and that Plavix was effective for all patients.

17. Therefore, the Court determines 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

18. The Supreme Court of Hawai‘i has already affirmed the original trial prior court's ruling that "Defendants committed unfair acts or practices[,]" both for violating public policy and engaging in immoral, unethical, and unscrupulous conduct. *Shikada, supra*, 152 Hawai‘i at 448, 526 P.3d at 425. As such, there are no additional conclusions of law that need to be determined by this Court with respect to Defendants' liability for unfair practices.

II. DEFENDANTS' AFFIRMATIVE DEFENSES

19. In their August 28, 2023, Trial Brief, filed as Docket No. 1885, Defendants raised several affirmative defenses which the Court addresses below. The Court will discuss the reasons why each of these defenses are unsuccessful.

A. Preemption Defense

20. In their Trial Brief Defendants argued that the State's UDAP claim is preempted by federal law related to the issues of platelet function testing and intermediate metabolizers. However, the Supreme Court affirmed the original trial court's order rejecting this defense, finding that "Defendants have not established it would have been impossible under federal law for them to add information about the poor responder issue to the Plavix label." *Shikada*, 152 Hawai‘i at 439, 526 P.3d at 416. Therefore, to the extent Defendants litigated this issue at the trial and appellate court levels, the Supreme Court has necessarily resolved that issue. To the extent Defendants failed to raise this precise articulation of the issue before the trial and/or appellate court level, it has been waived.

B. Duty to Test on the Deceptiveness Claim

21. Defendants raised as an affirmative defense that there is no duty to test under the deceptiveness claim and therefore their suppression of research is irrelevant to the State's deceptiveness claim under UDAP. However, this is not an affirmative defense and the Court is not persuaded. First, Defendants are the ones who presented evidence that they did not know about the issues related to Plavix resistance and CYP2C19 because they were not known by the larger scientific community. As such, the State is entitled and allowed under Hawai‘i law to rebut those claims by showing that the scientific community (apart from Defendants) did not know about these safety and efficacy issues because of Defendants' suppression of scientific research. Second, Defendants' suppression and failure to investigate the risks of Plavix resistance is directly relevant to penalties factors for the deceptiveness claim. As discussed below, one of the factors to consider in a penalties calculation under a statute such as UDAP is the good or bad faith of the defendant. The fact that Defendants deliberately engaged in a campaign to prevent

the development of science of a known risk that would have reduced the marketability of their drug for the sole purpose of protecting sales of that same drug, is highly probative to the penalties inquiry.

C. Penalties Defenses

22. Defendants also assert as affirmative defenses the claim that there is no authority for the Attorney General to bring a standalone UDAP claim for civil penalties. This issue has already been decided against Defendants on appeal. They made this argument to the Supreme Court of Hawai‘i, and the Court, by remanding this case for a determination of the amount of civil penalties to be awarded, necessarily rejected Defendants' argument.

23. Additionally, Defendants assert as an affirmative defense that violations based on a duty to study cannot stand under due process in the absence of a finding of harm. The Court is skeptical of Defendants' argument that harm is required, as Defendants cite no law to support their position. However, as discussed below and as found in the above factual findings, the Court has found harm in this case. As such, this defense is moot.

III. PENALTIES

24. 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.

A. Factors to Consider in Penalties Calculations

25. 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). In addition, courts also consider the factors of: (1) "the deterrence value of the assessed penalties" and (2) "the duration of the defendant's unlawful conduct." *Wilson*, 414 S.C. at 85, 777 S.E.2d at 203. Here, the Court considers each of these factors in turn in determining the civil penalties to impose on Defendants.

B. Penalties for Deceptiveness

i. *Reader's Digest* Factor

1. Good or Bad Faith of Defendants

26. The Court finds that the Defendants acted in bad faith during the relevant period of December 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 and efficacy risk with their drug. Defendants knew from the time of launch that there was a risk that about thirty percent of patients might have a diminished response to Plavix, but they did not update their label. Nothing in those regulations required a showing of any sort of association of "clinical outcomes" before making such updates, as Defendants argued. As early as 1998, Defendants also had knowledge of the involvement of CYP2C19 in the

metabolism of Plavix and the ability of its polymorphisms to prevent activation of other drugs, as well as Plavix's own issues with variability of response, before the drug was ever sold on the market. Yet, Defendants ignored these glaring warning signs and did nothing to warn patients or physicians. P0008 [Hebden Email, March 30, 2009].

27. From after launch until 2010—for over a decade—studies by outside investigators repeatedly affirmed Defendants' internal meta-analysis showing that approximately 30% of patients were poor responders to the drug. However, Defendants never updated the label until the FDA started asking questions about resistance. Defendants' internal documents clearly articulated the reason why: they feared the negative marketing implications. *Shikada* 152 Hawai'i at 448, 526 P.3d at 425. Rather than inform consumers about the issues related to the risk of diminished response, Defendants debated internally how to deal with the issue of Plavix resistance, discussing things like the "potential threat for future sales" as well as how it might "increase [the] risk of receiving questions from Health Authorities." P0811at PLAV_PP_BMS00284199 [2003 Action Plan]. Defendants also, instead of warning patients, developed a strategy for "shaping the market" by taking several actions including "challeng[ing] the links to clinical outcomes." P0430 at PLAV_BMS_00608286 [Wolf Email December 2, 2005]. Later Defendants discussed their view that resistance stood "as a threat to clopidogrel's future success on its own" in terms of "reimbursement, selective use, [and] efficacy image." P0433 at PLAV_JPP_BMS02495397 [2006 Variability of Response Strategic Workshop PowerPoint]. These are only two examples of Defendants' deceptiveness that were shown at trial. The Court finds Defendants' internal communications to be highly probative and damning.

28. From 1998 to March 2010, Defendants had the ability and knowledge necessary to update the Plavix drug label. Yet, they chose not to because they believed 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. Given the importance of the medical issues typically faced by a Plavix consumer, the significance and impact of Defendants' bad faith during the period of December 1998 to March 2010 is both substantial and deeply troubling.

2. Injury to the Public

29. 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 and efficacy 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, but a patient's inability to fully bioactivate the drug may still leave 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. Moreover, a lack of disclosure undermines the national guidelines, addressed at trial, that provide for shared decision making between the doctor and the patient.

30. Drug manufacturers have the best and most complete information about their drug, which is why there is a common law duty to keep abreast of developments and data regarding their drug, including information about safety risks, and strengthen label warnings, if necessary. For this reason, the public reasonably relies on these companies (as does the FDA) to timely disclose important information, including a lack of efficacy based on genetic factors. As found above, injury to the public has occurred given the evidence in this trial. Hawai‘i consumers and their prescribing physicians were denied material information by the drug manufacturer regarding the safety and efficacy of Plavix that was necessary in order for Plavix

patients to make informed choices among their treatment options. The fact that the injury is neither calculated nor quantified does not mean there is no injury.

31. Although this is not a medical malpractice case that directly implicates the Hawai‘i doctrine of informed consent, it is an analogous set of circumstances that raises the same concerns about a patient's human dignity, personal autonomy, and self-determination. It raises the question whether a consumer-patient is harmed when a drug company, rather than a doctor, decides to tell the consumer-patient only what the drug company wants the consumer-patient to know, rather than what the consumer-patient needs to know in order to make an informed decision about whether to take the drug or not, and if so, whether to take additional precautions to protect his or her health and safety if the drug fails to work properly.

32. While physical injury is not required to prove injury under this element, based on the totality of the evidence, the Court also finds that it is likely that Hawai‘i patients suffered major adverse cardiac events, in some cases fatal, because they did not get the intended anti-platelet effect from Plavix.

3. Desire to Eliminate the Benefits Derived from a Violation

33. The benefits derived by Defendants as a result of their material omissions from the Plavix label were substantial. After its launch in 1998, Plavix became a blockbuster drug for Defendants and the prescription of Plavix, often in conjunction with aspirin, became a goldmine for Defendants in the treatment of many cardiovascular conditions. Defendants were able to reap huge financial benefit from the success of Plavix, including from consumers within the State of Hawai‘i. P0359-0375 [BMS SEC Filings]; P0385-0394 [Sanofi SEC Filings]. These extraordinary revenues were generated in part as a result of Defendants' deceptive practices. 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. P0811 at PLAV_JPP_BMS00284199 [Action Plan July 2003]. The civil penalty calculations therefore must also account for the need to eliminate the benefits derived by Defendants from their use of deceptive business practices.

4. Necessity of Vindicating the Authority of the Agency Involved

34. The UDAP statute was enacted by the Hawai'i Legislature to act as a consumer protection measure and under HRS § 480-3.1 and 480-20(a), the Attorney General was given both the power and the responsibility 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 violation of UDAP, it is incumbent upon the Attorney General, as the chief law enforcement officer of the State, to protect the public's interest.

35. Remedial statutes, such as UDAP, are to be construed "to suppress the perceived evil and advance the enacted remedy." *Hawai‘i Cmty. Fed. Credit Union v. Keka*, 94 Hawai`i 213, 229, 11 P.3d 1, 17 (2000).

36. The Court finds that the State has a particularly strong interest in ensuring that drug companies operate legally, honestly and fairly in Hawai‘i and do not omit material information about pharmaceutical drugs from their labels, 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 a particularly high risk to patients of East Asian and Pacific Island descent, who represent a significant portion of Hawai‘i's population.

37. 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.

5. Defendants' Ability to Pay

38. 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 wrongdoer's financial ability to pay. Given that important purposes of statutes such as UDAP are to protect consumers and deter future unfair or deceptive conduct, the penalty must be of an amount that is appropriate for each particular defendant.

39. 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. *See United States v. ITT Continental Baking Co. ("ITT Continental Baking")*, 420 U.S. 223, 231 (1975). In *ITT Continental Baking*, the United States Supreme Court noted that in adopting the FTC Act, Congress was concerned with avoiding a situation where a statutory penalty would be regarded by violators as "nothing more than an acceptable cost of violation, rather than as a deterrence to violation." *Id*. The Court concludes that the same concern applies to awarding an appropriate penalty for the commission of unfair and deceptive trade practices under Chapter 480.

40. The Hawaii Legislature has already determined the fair range of penalties under § 480-3.1: to be between $500 and $10,000 per violation. Therefore, the Court must determine an amount within that range.

41. 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, BMS reported net sales of Plavix totaling $50.3 billion. P0359-P0384 [BMS SEC Filings]. In the financial filings with the SEC for years 2002 through 2012, Sanofi reported net sales from

Plavix totaling €22.1 billion.[22] P0385-P0403 [Sanofi SEC Filings]. Therefore, Defendants have the ability to pay an award appropriate to the egregiousness of their misconduct toward Hawai‘i consumers.

42. While all of the foregoing factors and considerations are important, in the circumstances of this case, the Court finds Defendants' bad faith, Defendants' ability to pay, the desire to eliminate benefits derived from violation, and the need to deter to be particularly compelling.

ii. What Constitutes a Violation

43. The Court finds that Defendants' deceptive conduct in this case was far-reaching and persistent. Based upon the evidence presented at trial and the above findings of fact and conclusions of law, the Court finds that the distribution of each copy of the Plavix label (package insert) with every retail prescription filled and refilled and non-retail units sold, in the State of Hawai‘i was a deceptive act or practice in violation of UDAP because each Plavix label omitted material safety and efficacy information and therefore had the capacity to mislead consumers.

44. Other courts applying the federal counterpart to Hawaii's UDAP statute—the FTC Act—and other statutes similar to UDAP have routinely found that each piece of material containing the deceptive statement was a separate and independent violation. *See e.g., United States v. Reader's Digest Ass'n, Inc.*, 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

[22] 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.

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); *State ex rel. Wilson v Ortho-McNeil-Janssen Pharmaceuticals, Inc.*, No. 07-CP-42-1438, 2011 WL 2185861 (S.C.Com.Pl. June 03, 2011).

45. Tallying the number of violations in terms of the retail prescriptions filled and nonretail units sold is appropriate given the circumstances of the deceptive acts in this case. The warnings, risks, and benefits listed in a drug's label are the 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." P0416. Every time a consumer of Plavix initially filled, or subsequently refilled a Plavix prescription, that consumer was deceived. As Dr. Roome acknowledged, it is important for prescribing doctors and patients to be fully informed as to the relevant scientific and medical information about a drug every time a prescription is filled and refilled. The label also notes that the information in the boxed warning is "the most important information [you] should know about Plavix[.]" P0412 [Plavix Label March 2010]; P0416 [Medication Guide May 2019]; P0833 [Plavix Label September 2022]. As such, the Court finds that each retail prescription, filled and refilled, and non-retail units sold in the State of Hawai'i constitutes a separate and distinct deceptive act in violation of UDAP. A per prescription penalty makes sense if the missing black box warning was material to consumers. *See Shikada*, 152 Hawai'i at 448.

46. 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. Defendants argued that the number of violations should be reduced only to the percentage of people that

were CYP2C19 poor metabolizers in Hawai‘i. The Court disagrees. There are poor responders among all races, and Defendants omitted material information from the labels of all Hawai‘i consumers of Plavix, thereby undermining their ability to give informed consent. Patients cannot know whether they are poor metabolizers until they get tested. The fact that Defendants withheld material information from all Hawai‘i consumers requires that Defendants be penalized for each and every Plavix label that omitted this critical risk information.

iii. Number of Violations and Penalty Amount

47. Given the evidence presented at trial, the factual findings affirmed by the Supreme Court, the above findings of fact, and the above conclusions of law, the 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 deceptive act or practice in violation of UDAP. Defendants argued that the penalties should be limited to prescriptions filled or refilled after the 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) (D1252 [Mega, 2009]), 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). D1194 [Hulot, 2006]. The Court is not persuaded by these arguments. As discussed above, the overwhelming weight of the evidence is that Defendants' deceptive business practices extended back to the launch of Plavix in December 1998. As such, the Court finds that the number of deceptive acts or practices violations resulting from the Defendants' joint misconduct is 834,012, as calculated by the State's expert Dr. Nicole Maestas.

48. Given the factors discussed above and the findings of fact, the Court concludes the appropriate penalty to be $1,000 per violation, for a total of $834,012,000 in civil penalties.

C. Penalties for Unfairness

49. As the Supreme Court affirmed on appeal, Defendants also committed unfair acts and practices in violation of UDAP, including the failure to investigate the poor responder issue, suppression of studies regarding that and related issues, and burying their heads in the sand. *Shikada, supra*, 152 Hawai‘i at 445-48, 526 P.3d at 422-25. This Court finds that those unfair acts or practices, which are based on separate conduct from that underlying Defendants' deceptive practices described above, constitute independent violations of UDAP for which penalties may also be imposed. *Id.* at 443, 526 P.3d at 420 ("*Unfair* act UDAP claims are distinct from deceptive act UDAP claims." (emphasis in original)).

50. This Court was tasked on remand with evaluating appropriate penalties for these unfair acts or practices.

i. *Reader's Digest* Factors

51. The *Reader's Digest* and other factors discussed above apply to unfair acts, as well as to deceptive acts. Because analysis of most of those factors is the same, whether applied to unfairness or deception, the Court need only examine Defendants' good or bad faith and injury to the public separately with respect to Defendant's unfair acts.

1. Good or Bad Faith of Defendants

52. The Court concludes that Defendants' unfair acts or practices were deliberate and pervasive, and they slowed and negatively affected the development of science related to Plavix for over a decade. The Court's findings show that—despite Dr. Roome's admission that the Defendants should know the pharmacology, strengths, and weaknesses of their own drugs better

than anyone—Defendants made and followed policies to reject any studies for fear of the development of literature relating to Plavix resistance. Further, when the scientific community began to independently discover the issues Defendants already knew, Defendants did not immediately take steps to ensure patient safety. Instead, they continued to deny the existence of Plavix resistance, choosing instead to rename the phenomenon to something they thought was less harmful to their marketing efforts, variability of response. They also avoided conducting any studies that might reveal how harmful Plavix resistance was to patients.[23] Then, cynically, Defendants later pointed to the absence of such studies as justification for their failure to update their label. By doing so, Defendants created and maintained a self-sustaining feedback loop that prevented the public from learning about Plavix's serious limitations. All of this was done to benefit Defendants' financial bottom line. The Court further notes that it rejects Defendants' argument that because Defendants developed an "action plan" supposedly to study Plavix variability of response in 2003, Defendants should be spared from imposition of a daily penalty for unfairness from June 2003 forward.

53. Document after document authored by Defendants showed that marketing and sales considerations were the reasons why studies were not done. The Supreme Court commented on Defendants' misconduct, stating that "[p]reventing risks from becoming apparent for financial gain offends Hawai‘i public policy." *Shikada*, 152 Hawai‘i at 447, 526 P.3d at 424.

[23] Defendants argued at length at trial that they were in fact performing studies. However, each study Defendants cited was either not designed or powered to determine how Plavix resistance, including CYP2C19 poor responders, led to increased rates of heart attacks and strokes, or the results came from negative trials (where Plavix was shown to have no benefit for the population studies) or in low-risk populations where the benefits of Plavix were marginal at best. Defendants' arguments that they were meaningfully studying the problem are not credible and are substantially outweighed by the State's evidence. Indeed, Dr. Gavin, BMS' Director of Medical Affairs, testified that they never conducted a study linking poor metabolizers and clinical outcomes. Court's Exhibit G at 116:16-20.

All of these facts show the extent of Defendants' significant and troubling bad faith as it relates to their unfair acts or practices.

2. Injury to the Public

54. In addition, the Court finds that Defendants' unfair conduct of suppressing studies caused substantial injury to Hawai‘i consumers. First, as discussed above, the record shows that the information related to Plavix resistance, including CYP2C19 poor responders, is material because such facts are important to a reasonable consumer. As such, the fact that the scientific research surrounding Plavix resistance was suppressed since before the drug was launched until the FDA mandated its inclusion in the Plavix label over a decade later creates a substantial injury to consumers. Second, the evidence shows that Plavix resistance caused harm to patients. Study after study linked Plavix poor responders to higher rates of heart attack and stroke while taking Plavix as compared to normal responders. Despite the mounting evidence regarding the link between poor responders and clinical outcomes from outside researchers, Defendants continued to bury their heads in the sand and ignore the issue. Again, the fact that the injury is neither calculated nor quantified does not mean that there is no injury.

55. Indeed, it is reasonable for the Court to find that Hawai‘i patient care involving Plavix would have been improved had Defendants put forth appropriate efforts to research Plavix resistance and its cause during that substantial time period and had they followed their duty to ensure the sufficiency of their label as soon as the risk of Plavix resistance became apparent. By suppressing research, Defendants created an environment where Hawai‘i prescribing physicians practiced for more than a decade without the necessary information needed to evaluate the serious limitations of this heart medication.

56. Defendants presented to the world the impression that Plavix would reduce the risk of heart attack and stroke. And for many people it obviously did. Even the State does not deny that. However, Defendants' campaign to suppress research, and their refusal to acknowledge the legitimacy of independent medical literature showing Plavix's safety and efficacy risks, resulted in an untold number of Hawai‘i patients taking a drug that may not have worked as well for them as intended, or may not have worked at all.

57. Defendants argued at trial that a finding of injury to consumers requires physical injury to the consumer. The Court disagrees for the reasons discussed herein.

58. Hawai‘i courts have always exhibited great respect for human dignity and personal autonomy of Hawaii's citizens. One example of that is the Hawai‘i courts' adoption of a patient-oriented standard of informed consent in which a patient must be told *not* what his or her doctor *thinks* he or she should be told, but what an objectively reasonable patient would need to know in order to make an informed decision about his or her medical treatment.

59. For the above-stated reasons, the Court finds that the *Reader's Digest* "injury to the public" factor has been met.

ii. Number of Violations and Penalty Amount for Unfairness Claim

60. In the *Shikada* decision, the Supreme Court of Hawai‘i suggested, but did not expressly decide, that an appropriate penalty for the kind of conduct that was found to be unfair in this case would be a daily penalty. *Shikada, supra*, 152 Hawai‘i at 449, 526 P.3d at 426 ("In these circumstances, an appropriate penalty would correlate more with the length of time the Defendants 'buried their heads in the sand.'"). In light of the above discussed factors and the Court's findings in this case, the Court concludes that a per-day penalty is appropriate for Defendants' unfair acts or practices.

61. As noted previously, approximately 4,100 days elapsed from the time of the Plavix launch in December 1998 to announcement of the Plavix boxed warning on March 12, 2010. In light of the substantial evidence discussed above, the Court finds that a daily penalty of $10,000 per day is warranted as to each of the Defendant groups.

D. Assessment of Penalties

62. Under Hawai‘i law, the Court acknowledges that the penalties under §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-Synethelabo 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 several against the Sanofi Defendants.

63. The Court finds substantial evidence in the record showing that both BMS and the Sanofi Defendants committed the unfair and deceptive practices as part of their Joint Venture.

64. Under the deceptiveness claim, the Court finds that Bristol-Myers Squibb and the Sanofi Defendants are equally responsible for each deceptive violation, and for each fill or refill of Plavix in Hawai‘i. The Court 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.

65. Under the unfairness claim, the Court finds that Bristol-Meyers Squibb and the Sanofi Defendants both committed the unfair acts and practices as affirmed by the Supreme Court of Hawai‘i. Based upon a time span of 4,100 days, the Court awards civil penalties of $41,000,000 against Defendant Bristol-Myers Squibb Company and civil penalties in the amount of $41,000,000, jointly and severally, against Defendants Sanofi-Aventis U.S. LLC, Sanofi US Services Inc., and Sanofi-Synthelabo Inc.

66. 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.

ORDER

IT IS HEREBY ORDERED, ADJUDGED AND DECREED that judgment shall be entered in favor of Plaintiff State of Hawai‘i and against (1) Defendant Bristol-Myers Squibb Company in the amount of $458,006,000, and (2) Defendants Sanofi-Aventis U.S. LLC, Sanofi US Services Inc., and Sanofi-Synthelabo Inc., jointly and severally, in the amount of $458,006,000.

DATED: Honolulu, Hawai‘i, May 21, 2024.

/s/ James H. Ashford

JUDGE OF THE ABOVE-ENTITLED COURT