

**IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF PENNSYLVANIA**

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<b>IN RE: AVANDIA MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION</b>	:	
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	:	<b>MDL No. 1871</b>
	:	<b>07-md-01871</b>

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<b>THIS DOCUMENT APPLIES TO: ALL ACTIONS</b>	:	
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**MEMORANDUM OPINION & ORDER**

**RUFE, J.**

**September 7, 2011**

This MDL action arises from injuries allegedly suffered by patients who were prescribed Avandia—an FDA-approved diabetes medication. In 2007, the United States Judicial Panel on Multidistrict Litigation transferred thousands of individual cases to this Court for consolidated pre-trial proceedings. The cases allege that Avandia (and its sister drugs Avandamet and Avandaryl) cause an increased risk of heart attack, heart failure, and other physical injury, and that manufacturer GlaxoSmithKline (“GSK”) failed to adequately warn of those risks.<sup>1</sup> Before the Court is GSK’s Omnibus Motion for Summary Judgment on the adequacy of Avandia’s label warnings regarding congestive heart failure (“CHF”).<sup>2</sup> It seeks dismissal of claims brought by plaintiffs from New York, Florida, Texas and Pennsylvania who suffered CHF-related injuries

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<sup>1</sup> In re Avandia Mktg., Sales Practices & Prods. Liab. Litig., 528 F. Supp. 2d 1339 (J.P.M.L. 2007).

<sup>2</sup> Congestive heart failure is a ventricular dysfunction, in which the heart’s ability to pump blood to meet the body’s metabolic needs is impaired, the symptoms of which include dyspnea (shortness of breath) and edema (fluid retention in body tissue), among others. See, e.g., The Merck Manual 652–60 (18th ed. 2006); Harrison’s Principles of Internal Medicine 1318–23 (15th ed. 2001). This motion addresses only claims in which CHF, rather than myocardial infarction, is the alleged primary injury. See GSK Reply [doc. no. 1403] at 1 n.1.

and who ingested Avandia after February 8, 2001<sup>3</sup>—the date on which GSK amended the Avandia package insert to include CHF-related risk information. In the alternative, GSK seeks summary judgment on the adequacy of Avandia’s label as revised on August 14, 2007 as to all plaintiffs from New York, Florida, Pennsylvania, and Texas who ingested Avandia after that date.<sup>4</sup> The Plaintiffs’ Steering Committee (“PSC”) opposes the motion on its merits, and also urges denial, pursuant to Rule 56(d) of the Federal Rules of Civil Procedure, because insufficient discovery on CHF-related issues to date prevents it from presenting disputed facts essential to support its opposition.

The Avandia label adopted on February 8, 2001 generally warned that Avandia, like other drugs of its class, when used alone or with other antidiabetic agents, causes fluid retention, which can exacerbate or lead to CHF; that patients should be observed for signs and symptoms of heart failure; that Avandia should be discontinued upon deterioration of cardiac status; that Avandia should be used cautiously in patients with edema or at risk for heart failure; and that, in postmarketing experience, incidents of CHF had been reported. The 2007 label included the same or similar warnings with additional detail from clinical trials regarding risks for specific patient subpopulations, but also included a prominent boxed warning that Avandia directly causes CHF in some patients. GSK’s motion presents a single question: Did the format and content of the 2001 and 2007 labels, as a matter of law, adequately warn of CHF risks? Because the PSC has presented sufficient evidence of labeling omissions regarding CHF risks, including

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<sup>3</sup> GSK asserts that there are at least 63 filed and tolled cases in which Plaintiffs from these states seek damages for CHF-related injuries based on ingestion of Avandia after February 8, 2001. GSK Reply at 1 n.2.

<sup>4</sup> GSK Reply at 14–15.

those concerning certain patient subpopulations and sufficient evidence that GSK knew or should have known about those risks well before the labels disclosed them, as well as evidence of inconsistencies and ambiguities within the 2001 label, the Court finds that a reasonable jury could conclude that the labels were incomplete, inaccurate, or misleading as to CHF risks. Thus, the issue cannot be resolved as a matter of law and summary judgment on the adequacy of the labels is inappropriate.

## **I. FDA LABELING REQUIREMENTS & AVANDIA LABEL REVISIONS**

### **A. FDA Labeling Requirements**

When the FDA approves a new drug application, it also approves the drug's labeling, which must be used verbatim.<sup>5</sup> The "label," as used by the Court here, is also known as the "package insert" or "professional labeling," and is intended for use by health care practitioners, not patients. The label includes a range of information necessary for safe and effective use.

The FDA requires specific content and a particular format for prescription drug labels.<sup>6</sup> The agency may also require the label to include, at a location specified by the agency, a prominently displayed "boxed warning" that highlights risks that may lead to death or serious injury that are more fully described elsewhere in the label.<sup>7</sup> Also known as a "black box

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<sup>5</sup> Wyeth v. Levine, 129 S. Ct. 1187, 1196 (2009) (citing 21 U.S.C. § 355; 21 C.F.R. § 314.105(b) (2008)).

<sup>6</sup> See 21 C.F.R. §§ 201.56(e)(1), 201.80 (requirements for older prescription drug products). Drugs approved on or after June 30, 2001 must comply with the content and format requirements under 21 C.F.R. § 201.56(d). Section 201.80, amended on January 24, 2006, includes largely the same content and format requirements as former Section 201.57. See Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922-01, 3928 (Jan. 24, 2006). Manufacturers of older products may voluntarily elect to conform to the labels for such drugs to the content and format applicable to newer drugs by submitting a supplement with proposed labeling. Id.

<sup>7</sup> 21 C.F.R. §§ 201.80(e), 201.57(c)(1).

warning,” it is the strongest warning available.<sup>8</sup>

Additionally, for drugs approved before June 30, 2001, including Avandia, sections of the label relevant to risk information must be presented under the following headings and in the following order: Contraindications, Warnings, Precautions, and Adverse Reactions.<sup>9</sup> The risk information sections must appear after sections on drug description, clinical pharmacology, and indications and usage.<sup>10</sup>

These risk information sections reflect, in descending order, the seriousness of the risks identified in each category.<sup>11</sup> For example, the “Warnings” and “Contraindications” sections must identify any potentially fatal adverse reactions.<sup>12</sup> “Contraindications” caution use where the risks outweigh the benefits, such as use in patients hypersensitive to the drug or with particular vulnerabilities that pose a substantial risk of harm from the drug.<sup>13</sup> The “Warnings” section must describe any serious adverse reactions and potential safety hazards, treatment limitations that might be required by those risks, and advice as to steps that should be taken if the adverse event occurs. The “Warnings” section should also be updated with new warnings when there is

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<sup>8</sup> Ackermann v. Wyeth Pharm., 526 F.3d 203, 211 n.12 (5th Cir. 2008); N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC Inc., 537 F.3d 35, 42 (1st Cir. 2008).

<sup>9</sup> See 21 C.F.R. § 201.80. For newer drugs, the Warnings and Precautions sections are combined. See id. § 201.57(c)(6).

<sup>10</sup> See id. § 201.80. For newer drugs, these sections must appear after a highlights section and sections on indications and usage, dosage and administration, and dosage forms and strengths under the full prescribing information. See id. § 201.57.

<sup>11</sup> See, e.g., Martin v. Hacker, 628 N.E.2d 1308, 1312 (N.Y. 1993).

<sup>12</sup> 21 C.F.R. § 201.80(g)(3).

<sup>13</sup> Id. § 201.80(d).

evidence of an association, rather than causation, with a serious hazard.<sup>14</sup> The “Precautions” section requires information about special care practitioners should use when treating patients with the drug, and should include information regarding study results that may be helpful to practitioners in monitoring patients and identifying adverse reactions.<sup>15</sup> Finally, the “Adverse Reactions” section requires disclosure of “undesirable effect[s], reasonably associated” with the drug.<sup>16</sup> But this section should include “only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”<sup>17</sup> The “Adverse Reactions” section should reflect information from the entire safety data base, including clinical studies as well as postmarketing experience, which includes information compiled from spontaneous adverse event reports (“AERs”).<sup>18</sup> Manufacturers may make claims “comparing the drug . . . with other drugs in terms of frequency, severity, or character of adverse reactions” in this section only if the findings are “based on adequate and well-controlled studies.”<sup>19</sup>

Finally, FDA regulations permit “a manufacturer . . . to add or strengthen a contraindication, warning, precaution, or adverse reaction” without receiving prior FDA approval, by filing a “changes being effected” supplement with the FDA.<sup>20</sup>

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<sup>14</sup> Id. §201.80(e).

<sup>15</sup> Id. § 201.80(f)(1), (3).

<sup>16</sup> Id. § 201.80(g).

<sup>17</sup> Id. § 201.57(c)(7).

<sup>18</sup> See id. §§ 201.80(g)(2), 201.57(c)(7)(ii)(B).

<sup>19</sup> Id. §§ 201.57(c)(7)(iii); 201.80(g)(4).

<sup>20</sup> Levine, 129 S. Ct. at 1196 (citing 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C)) (internal quotations omitted).

## **B. Avandia Label Revisions**

Avandia, the brand name for rosiglitazone maleate, was approved by the Food and Drug Administration in 1999. It is a member of a class of drugs known as thiazolidinediones (“TZDs”), used to manage non-insulin-dependent diabetes, or Type 2 diabetes.<sup>21</sup> Avandia competes with Actos, the brand name for pioglitazone, the only other competitor TZD currently on the market.

The Food and Drug Administration (“FDA”) first approved Avandia for use only as monotherapy or in combination with metformin, another diabetes medication.<sup>22</sup> The “Precautions” section of the first Avandia labels, in 1999, warned that the drug should be used cautiously in patients with edema—a condition in which large amounts of fluid accumulate in subcutaneous tissue;<sup>23</sup> that TZDs can cause fluid retention, which can exacerbate CHF; that preclinical studies showed TZDs caused plasma volume expansion and cardiac hypertrophy;<sup>24</sup> and that Avandia was not indicated for patients with moderate or severe symptoms of heart failure (i.e., New York Heart Association (“NYHA”) Class 3 or 4 status) because such patients had not been studied.<sup>25</sup> The label was subsequently revised several times—in 2001, 2005, 2006,

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<sup>21</sup> See Mem. in Supp. of Defendant [GSK’s] Omnibus Mot. for Summ. J. with Respect to Pls. Who Developed Congestive Heart Failure & Used Avandia After Feb. 2001 (“GSK Mem.”) [doc. no. 912], Ex. A (May 1999 Package Insert).

<sup>22</sup> GSK Mem., Ex. B at 11.

<sup>23</sup> See Dorland’s Med. Dict., 600 (31st ed. 2007).

<sup>24</sup> Cardiac hypertrophy is an abnormal enlargement of the heart muscle, due, in some cases, to volume and pressure overload. See id. at 910.

<sup>25</sup> See GSK Mem., Exs. A, B.

The NYHA classification indicates the stage of heart failure. Classes 3 and 4 indicate moderate to severe symptoms of heart failure, respectively. The term “contraindicated” generally means that the use is not advised

2007, and 2011—to include increasingly detailed, and, ultimately, heightened warnings about CHF and other risks.

The dispute here centers on the adequacy of CHF warnings in the 2001 and 2007 Avandia label revisions. Because the FDA’s labeling format and content requirements and GSK’s various label revisions provide important context, the Court details them below.<sup>26</sup>

### 1. *The February 8, 2001 Avandia Label*

On February 8, 2001, GSK revised the label to include another indication: use in combination therapy with sulfonylureas, another type of diabetes medication, in addition to the prior indication for monotherapy and Avandia+metformin therapy.<sup>27</sup> The 2001 label also included, in the Warnings section, a class-wide warning that Avandia, like all TZDs, can cause fluid retention, which in turn can lead to or exacerbate CHF. This new class-wide warning thus expanded the prior warning about fluid retention in the “Precautions” section by including it in the more prominent “Warnings” section of the label and by indicating fluid retention can both exacerbate as well as lead to CHF. It also warned that Avandia was not recommended for patients with NYHA Class 3 and 4 cardiac status. The 2001 revision additionally included, in the “Adverse Events” section, clinical trial results that showed an increased incidence of edema in Avandia monotherapy as well as increased CHF risks from Avandia+insulin therapy, and warned

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because the harm will outweigh the benefit. *See Dorland’s*, *supra* note 23, at 417 (a contraindication is a condition which renders a line of treatment improper or undesirable). A drug is indicated for a condition if its use for treatment of that condition is medically appropriate. The FDA approves drugs for particular indications. To say a drug is “not indicated” for a particular type of patient or condition, however, says little about its risks.

<sup>26</sup> The Court makes no determination here about the admissibility of the labels. Admissibility in any individual case will depend upon whether a particular label was revised before or after a particular plaintiff’s cause of action arose and the purpose for which it is offered. *See* Fed. R. Evid. 407.

<sup>27</sup> *Compare* GSK Mem. Ex. B (1999 Label) at 11, *with* Ex. C (Feb. 8, 2001 Revised Label) at 12–13.

that Avandia+insulin therapy was not indicated. The label did not include clinical trial results for combination therapy with metformin or sulfonylurea. The 2001 revision included the following statements:<sup>28</sup>

#### **WARNINGS**

**Cardiac Failure and Other Cardiac Effects:** Avandia, like other [TZDs], alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. Avandia should be discontinued if any deterioration in cardiac status occurs.

Patients with [NYHA] class 3 or 4 cardiac status were not studied during the clinical trials. Avandia is not recommended in patients with NYHA class 3 or 4 cardiac status.

In two 26-week U.S. trials . . . Avandia plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including . . . congestive heart failure (2.5%). In these . . . clinical studies, an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on AVANDIA and insulin combination therapy . . . . Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg. daily dose of Avandia. . . . Three of the 10 patients who developed cardiac failure on combination therapy . . . had no known prior evidence of congestive heart failure or pre-existing cardiac condition. **The use of Avandia . . . in combination therapy with insulin is not indicated . . . .**

#### **PRECAUTIONS**

**Edema:** Avandia should be used with caution in patients with edema.

. . . .  
Since [TZDs], including [Avandia], can cause fluid retention, which can exacerbate or lead to congestive heart failure, Avandia should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure . . . .

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with Avandia, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and Avandia . . . .

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<sup>28</sup> GSK Mem., Ex. C at 13–17 (bolding in original).



The “Adverse Reactions” section of the label also reported, in table form, adverse events identified in clinical trials: upper respiratory tract infection, injury, headache, back pain, hyperglycemia, fatigue, sinusitis, diarrhea and hypoglycemia.<sup>29</sup> The label reported the increased incidence of edema in double-blind studies of Avandia monotherapy compared to metformin and sulfonylurea (“SU”) monotherapies. Immediately thereafter it stated that reports of adverse experiences with Avandia monotherapy were similar for SU+Avandia and metformin+Avandia dual combination therapy, without reporting clinical trial data. It also reported study results for insulin+Avandia combination therapy that identified higher rates of edema and CHF compared to monotherapy. Finally, it identified adverse events seen in postmarketing experience. The Adverse Reactions section stated:<sup>30</sup>

There were a small number of patients treated with Avandia who had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with Avandia.

....

Edema was reported in 4.8% of patients receiving Avandia compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when Avandia was used in combination with sulfonylurea or metformin were similar to those during monotherapy with Avandia.

....

[E]dema was reported with higher frequency in the Avandia plus insulin combination trials . . . . Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with Avandia.

In postmarketing experience with Avandia, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported.<sup>31</sup>

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<sup>29</sup> GSK Mem., Ex. C at 21, Table 7.

<sup>30</sup> GSK Mem., Ex. C. at 20–22.

<sup>31</sup> GSK Mem., Ex. C. at 21–22.

## 2. 2005 Revised Labels

In August 2005, the label was apparently again revised<sup>32</sup> to include in the “Adverse Reactions” section new clinical trial results suggesting higher risks of edema from SU+Avandia combination therapy. The prior statement regarding the similarity of the adverse experiences reported for monotherapy and those for metformin+Avandia or SU+Avandia combination therapy remained, but now appeared *before* the data on Avandia monotherapy and edema, rather than directly after it. The revised label stated:<sup>33</sup>

### **ADVERSE REACTIONS**

#### **Trials of Avandia as Monotherapy and in Combination with Other Hypoglycemic Agents**

....

Overall, the types of adverse experiences reported when Avandia was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with Avandia. . . .

....

The reporting rate of edema was higher for Avandia 8 mg in sulfonylurea combinations (12.4%) compared to other combinations with the exception of insulin. Edema was reported in 14.7% of the patients receiving Avandia in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of [CHF] occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with Avandia. . . .

In December 2005, the “Warnings” section of the label was again revised to advise physicians that in addition to monitoring all patients for signs and symptoms of fluid retention, they should do so particularly for patients receiving combination therapy with insulin or SU, as well as for patients at risk for heart failure and those with NYHA Class 1 or 2 stage heart

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<sup>32</sup> The PSC suggests the label revisions discussed below occurred sometime in “late 2005 or early 2006,” citing to Avandia labels dated August 2005 and December 2005.

<sup>33</sup> Mem. in Supp. of the PSC’s Opp’n to GSK’s Omnibus Mot. for Summ. J. (“PSC Resp.”), Ex. 30 (August 2005 revised label) at 23.

failure.<sup>34</sup> Prior labels had provided only the more generalized advice that “[p]atients should be monitored for signs and symptoms of fluid retention;” they had not addressed NYHA stages of heart failure beyond concerns regarding patients with NYHA Class 3 and 4 stage heart failure, and had addressed concerns regarding combination therapy only with respect to insulin+Avandia. The new Warning stated:<sup>35</sup>

**WARNINGS**

**Cardiac Failure and Other Cardiac Effects:** Avandia, like other [TZDs], alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. All patients, particularly those receiving concurrent sulfonylurea or insulin therapy, those at risk for heart failure, and those with mild to moderate heart failure (New York Heart Association Class 1 or 2), should be monitored for signs and symptoms related to fluid retention, including heart failure. In combination with insulin, [TZDs] may also increase the risk of other cardiovascular adverse events. Avandia should be discontinued if any deterioration in cardiac status occurs.

Additionally, the Adverse Reactions section added the following statement regarding heart failure and SU+Avandia combination therapy: “[A]n increased incidence of heart failure has also been observed when Avandia was added to a sulfonylurea or to a sulfonylurea plus metformin.”<sup>36</sup>

**3. May 2006 Revised Label**

In May 2006, GSK again revised the “Warnings” section of the label to include the results of a clinical trial known as “Study 211,” a 52-week double-blind study of Avandia in Type 2 diabetic patients with NYHA Class 1 and 2 stage heart failure. It was apparently the first study

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<sup>34</sup> NYHA Class 1 and 2 stage heart failure indicates mild symptoms of heart failure—that is no, or only slight, limitations on physical activity, and comfort at rest.

<sup>35</sup> PSC Resp., Ex. 29 (Dec. 2005 Revised Label) at 14.

<sup>36</sup> PSC Resp., Ex. 29 at 23.

of Avandia in patients with both diabetes and diagnosed heart failure.<sup>37</sup> The study evaluated both adjudicated events<sup>38</sup> as well as investigator-reported, non-adjudicated events. The May 2006 label included the results in the Warnings section of the label, reporting a higher incidence of the following adjudicated cardiovascular endpoints: cardiovascular death, cardiovascular hospitalization, CHF worsening, new or worsening edema, new or worsening dyspnea, and increases in CHF medication.<sup>39</sup> It also reported unadjudicated endpoints for only ischemic adverse events, including myocardial infarction and angina, but excluded unadjudicated investigator-reports of CHF.

#### **4. 2007 Revised Labels**

In August and November 2007, GSK again revised the label to include a boxed warning as well as a contraindication for use in NYHA Class 3 or 4 stage patients, and a statement that Avandia was not recommended for any patient with symptomatic heart failure. The label also included, for the first time, a direct-causation statement for TZDs and CHF; prior labels had identified fluid retention as the primary effect. The August 2007 boxed warning stated, in part:<sup>40</sup>

#### **WARNINGS: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA**

- [TZDs], including [Avandia], cause or exacerbate congestive heart failure in some patients. After initiation of Avandia, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and or edema). If these signs and symptoms develop, the

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<sup>37</sup> PSC Resp., Ex. 57 at 1.

<sup>38</sup> An adjudicated event is one in which events are classified as falling into a particular category based on pre-defined criteria. Investigator-reported events do not necessarily adhere to those criteria.

<sup>39</sup> PSC Resp., Ex. 61 (May 2006 revised label) at 14–15.

<sup>40</sup> PSC Resp., Ex. 71 (August 2007 revised label).

heart failure must be managed according to current standards of care. Furthermore, discontinuation or dose reduction of Avandia must be considered.

- Avandia is not recommended in patients with symptomatic heart failure. Initiation of Avandia in patients with established NYHA Class III or IV heart failure is contraindicated.

Thus, not only did the warnings become more prominent, but the label included stronger language related to CHF: (1) a direct causation statement—that TZDs “cause or exacerbate” congestive heart failure in some patients; (2) the omission of the qualifying language that TZDs “*can* cause fluid retention” which “*may* exacerbate or lead to [CHF],” thus acknowledging that TZDs might directly cause CHF, rather than just edema, which, in turn leads to CHF; and (3) a contraindication for those with severe or moderate heart failure, rather than the prior statement that use was “not recommended” for such patients. The November 2007 revision added to the boxed warning a summary of the results of “ICT-42”—an integrated data set from 42 clinical trials—regarding risk of myocardial ischemic events, and included more detailed results in the Warnings section in the label as well.<sup>41</sup>

Due to concerns about the elevated risk of cardiovascular events in patients treated with Avandia, in September 2010, the FDA restricted use of Avandia to Type 2 diabetes patients who could not control their diabetes with other medications.<sup>42</sup>

### **5. February 2011 Revised Label**

GSK again revised the Avandia label in February 2011, after it filed the pending omnibus motion for summary judgment, to add to the Warnings and Precautions section results from three

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<sup>41</sup> PSC Resp., Ex. 65 (November 2007 revised label).

<sup>42</sup> Press Release, Food and Drug Administration, FDA significantly restricts access to the diabetes drug Avandia (Sept. 23, 2010) available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/UCM226975.html>.

clinical studies that showed, for patients age 65 and older, a statistically increased risk of heart failure requiring hospitalization from Avandia compared to Actos.<sup>43</sup> This was the first label that indicated that there was a CHF risk that may be particular to Avandia, distinguishable from purely class-wide effects. The label also stated, however, that a study of patients with an average age of 54, which included subpopulations of patients over age 65, did not find a heightened risk for Avandia users. The label retained the overall class-wide warning—that Avandia, like all TZDs, causes congestive heart failure in some patients.

## II. STANDARD OF REVIEW

Under Federal Rule of Civil Procedure 56(c), a court may grant summary judgment only “if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.”<sup>44</sup> A fact is “material” if it could affect the outcome of the suit, given the applicable substantive law.<sup>45</sup> A dispute about a material fact is “genuine” if the evidence presented “is such that a reasonable jury could return a verdict for the nonmoving party.”<sup>46</sup>

A party moving for summary judgment has the initial burden of supporting its motion by reference to admissible evidence<sup>47</sup> showing the absence of a genuine dispute of a material fact or that there is insufficient admissible evidence to support the fact.<sup>48</sup> Once this burden has been

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<sup>43</sup> PSC Resp., Ex. 73.

<sup>44</sup> Fed. R. Civ. P. 56(a).

<sup>45</sup> Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986).

<sup>46</sup> Id.

<sup>47</sup> Callahan v. A.E.V., Inc., 182 F.3d 237, 252 n.11 (3d Cir. 1999).

<sup>48</sup> Fed. R. Civ. P. 56(c).

met, “the non-moving party must rebut the motion with facts in the record and cannot rest solely on assertions made in the pleadings, legal memoranda, or oral argument.”<sup>49</sup>

In considering a summary judgment motion, the Court does not weigh the evidence or make credibility determinations; “the evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in [its] favor.”<sup>50</sup>

### III. DISCUSSION

GSK argues that its 2001 revised label was adequate as a matter of law both in 2001 and at all times thereafter because it accurately described the state of scientific knowledge in 2001, expressly and prominently warned about the increased risk of CHF from fluid retention and of the association between fluid retention and CHF within the Warnings and Precautions sections, advised that the risk of fluid retention applied whether Avandia was used alone or in combination with *any* antidiabetic agent, directed physicians to observe *all* patients for signs of heart failure, advised caution for use in patients with edema or symptoms of heart failure, and, in the Adverse Reactions section, identified a higher incidence of edema from Avandia monotherapy, and stated that CHF had been reported in postmarketing experience. GSK argues that regardless of what it later came to know, because of these warnings, the label is adequate as a matter of law for any plaintiff from Florida, New York, Pennsylvania and Texas—because of their similar adequacy standards—who ingested Avandia and suffered CHF-related injuries after adoption of the 2001

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<sup>49</sup> Berkeley Inv. Grp. Ltd. v. Colkitt, 455 F.3d 195, 201 (3d Cir. 2006).

<sup>50</sup> Anderson, 477 U.S. at 255.

label.<sup>51</sup> In the alternative, GSK argues that summary judgment is warranted for all claims arising after the August 2007 label revision, when the direct causation warning was provided in the most prominent way possible—via a boxed warning.

The PSC responds with evidence it claims would allow a reasonable jury to conclude the 2001 label was inadequate both in 2001 and thereafter until the 2011 label revision, because it did not reflect the true scope and nature of CHF risks. Except where otherwise noted below, GSK does not challenge the PSC's evidence. Instead it contends that the 2001 label (or at least the 2007 label), regardless of the evidence presented, was sufficiently complete and accurate to adequately warn physicians of CHF risks.

**A. The Standard for Adequacy of a Warning**

GSK proffers an adequacy standard, that, although both appealing and elegant on its face, is overly simplistic and ultimately inapplicable to the facts of this case. It asserts that a warning is adequate as a matter of law where it identifies the risk of the injury complained of, prominently displays that warning, and provides specific, detailed and scientifically accurate information regarding that risk based on then available scientific information, regardless of what it knows or later comes to know and whether it fails to include additional risk information providing context and specificity to that warning.<sup>52</sup> Though GSK concedes, as it must, that a warning is adequate only if it accurately conveys the scope and nature of the risk,<sup>53</sup> it glosses over the implications of

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<sup>51</sup> See GSK Mem. at 8–10; Tr. 245–50 (asserting that a manufacturer's warning, not its conduct, determines the adequacy of the warning and that though more detail was added to the label regarding CHF risks, the 2001 label remained adequate because of the generality of the warning as to all patients).

<sup>52</sup> GSK Mem. at 8–10; GSK Reply at 7.

<sup>53</sup> GSK Mem. at 8.



the “scope and nature” requirement as it must be applied to these cases.

As an initial matter, except in unusual circumstances, adequacy is ordinarily a question of fact. In three of the four states at issue (Florida, New York and Texas), the adequacy of a warning to a physician<sup>54</sup> is ordinarily left to the jury, unless the warning so clearly and accurately conveys the risk of the complained-about injury that reasonable persons could not disagree as to the adequacy of that label.<sup>55</sup> And though under Pennsylvania law, adequacy is initially a question of law,<sup>56</sup> where fact questions exist (e.g., regarding the sufficiency of the warning for a particular risk identified in the label and whether the warning was diluted by marketing representations), the question of adequacy is one for the jury.<sup>57</sup>

Though there are semantic differences in the applicable standard for adequacy in the four states, to find a label adequate as a matter of law, each state requires that the label accurately and unambiguously convey the scope and nature of the risk, with sufficient specificity given the

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<sup>54</sup> The Parties do dispute that all four states have adopted the learned intermediary doctrine for failure-to-warn cases involving prescription drugs. See, e.g., Martin v. Hacker, 628 N.E.2d 1308, 1311 (N.Y. 1993); Felix v. Hoffmann-LaRoche, Inc., 540 So. 2d 102, 104 (Fla. 1989); Gravis v. Parke-Davis & Co., 502 S.W.2d 863, 870 (Tex. Civ. App. 1973); Incollingo v. Ewing, 282 A.2d 206, 220 (Pa. 1971), *abrogated on other grounds as recognized in* Slaseman v. Myers, 455 A.2d 1213, 1218 (Pa. Super. Ct. 1983).

<sup>55</sup> McNeil v. Wyeth, 462 F.3d 364, 368 (5th Cir. 2006) (applying Texas law) (citing Williams v. Upjohn Co., 153 F.R.D. 110, 114 (S.D. Tex. 1994)); Felix, 540 So.2d at 105 (adequacy of drug warning is question of fact where reasonable people could disagree as to the adequacy of the warnings); Cooley v. Carter-Wallace Inc., 102 A.D.2d 642, 642 (N.Y. App. Div. 1984) (adequacy of warning is, in all but the most unusual circumstances, a question of fact to be determined at trial).

<sup>56</sup> Mazur v. Merck & Co., Inc., 964 F.2d 1348, 1366 (3d Cir. 1992) (“Under Pennsylvania law the determination whether a warning is adequate is a question of law.”) (citing Mackowick v. Westinghouse Elec. Corp., 575 A.2d 100, 102 (Pa. 1990)); Demmler v. SmithKline Beecham Corp., 671 A.2d 1151, 1154 (Pa. Super. Ct. 1996).

<sup>57</sup> Incollingo, 282 A.2d at 220 (holding “whether or not the warnings on the cartons, labels, and literature of [manufacturer] . . . were adequate, and whether or not the . . . warning [was] in effect cancelled out” by marketing information were questions properly for the jury).

particular of the risk at issue.<sup>58</sup> For example, under New York law, a warning is adequate as a matter of law if it “provides specific detailed information on the risks of the drug.”<sup>59</sup> But whether information is specific and detailed depends on whether the information is: accurate, that is, correct, fully descriptive and complete and conveys updated information as to all of the known or knowable risks; and clear, that is, whether the risk information is direct, unequivocal and sufficiently forceful to convey the risk, consistent on its face and not otherwise obscured by inconsistencies or contradictory statements in different sections of the label.<sup>60</sup> Similarly, in Florida, only where the label is accurate, clear and unambiguous, may a court find adequacy as a matter of law.<sup>61</sup> Under Texas law, although a warning may be adequate as a matter of law where it “specifically mentions the circumstances complained of,”<sup>62</sup> a generalized warning of a particular risk is not adequate as a matter of law when the label is not sufficiently specific, such as where it omits important information about the severity of a particular risk,<sup>63</sup> or significantly

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<sup>58</sup> The PSC argued in briefing that significant differences in the adequacy standards and theories of liability adopted by the four states and the need for a complex choice of law analysis precluded consideration of GSK’s omnibus motion. To be sure there are some differences in the standards, but, as the PSC conceded at oral argument, Tr. 240–42, for purposes of this motion, the standards are sufficiently similar.

<sup>59</sup> Martin, 628 N.E.2d at 1312.

<sup>60</sup> Id.

<sup>61</sup> Felix, 540 So. 2d at 105.

<sup>62</sup> Rolen v. Burroughs Wellcome Co., 856 S.W.2d 607, 609 (Tex. App.1993).

<sup>63</sup> See Jordan v. Geigy Pharm., 848 S.W.2d 176, 182 (Tex. App. 1992) (though label warned that drug reduced renal blood flow and could result in overt renal failure and that significant renal failure was observed in postmarketing experience, label was not adequate as a matter of law where it did not warn of risks of *acute or irreversible* renal failure and suggested that discontinuation of treatment may produce renal recovery).

understates the risk level.<sup>64</sup> Finally, under Pennsylvania law, factually accurate statements of fact regarding a particular risk are not adequate as a matter of law where there are disputes over whether the warning was sufficiently explicit and detailed.<sup>65</sup>

Additionally, the adequacy of the label cannot be determined solely by looking at the form and content of the label and the state of the scientific knowledge at the time the label was issued. Rather, in all four states, the adequacy of a warning is determined based on what a manufacturer knew or should have known about a given risk at the time a patient is prescribed the drug or the cause of action arose, and whether the label warned of that risk.<sup>66</sup> A manufacturer

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<sup>64</sup> See McNeil, 462 F.3d at 368 (under Texas law, where a label understates the risk, and the difference is significant, the potential misleading impact is a question for the jury).

At least one Texas court has adopted an exception to the learned intermediary doctrine based on direct-to-consumer (“DTC”) advertising. Centocor, Inc. v. Hamilton, 310 S.W.3d 476, 508 (Tex. App. 2010) (“[W]e hold that when a pharmaceutical company directly markets to a patient, it must do so without fraudulently misrepresenting the risks associated with its product.”). The PSC has not, however, presented evidence of any DTC promotion of Avandia. In addition, Texas law creates a rebuttable presumption that an FDA-approved label is adequate. See Tex. Civ. Prac. & Rem. § 82.007. But GSK does not move for summary judgment on that basis.

<sup>65</sup> Incollingo, 282 A.2d at 212 (though warning that drug was a potent therapeutic agent associated with blood dyscrasias, that blood studies should be conducted on patients, and the drug should not be used for minor infections “were correct statements of fact as far as they went,” question of adequacy of blood dyscrasia warning was appropriately submitted to the jury where there were disputes over, *inter alia*, whether warnings were sufficiently explicit and “went far enough in describing the dangerous potential toxicity of the drug”).

<sup>66</sup> See, e.g., Martin, 628 N.E.2d at 1311 (“The manufacturer’s duty is to warn of all potential dangers in its prescription drugs that it knew, or, in the exercise of reasonable care, should have known to exist.”); Lance v. Wyeth, 4 A.3d 160, 167 (Pa. Super. Ct. 2010) (“[A] manufacturer has a post-sale duty to warn of any dangerous side effects produced by its drugs of which it knows or has reason to know as long as its drugs are sold on the market.”) (citation and internal quotations omitted); Tenuto v. Lederle Labs., 695 N.Y.S.2d 259, 263 (N.Y. Sup. Ct. 1999) (duty of a drug producer or drug seller to warn of a particular risk only attaches at the time that such party knew, or should have known, of the risk in question; knowledge must be determined at the time of use or at the time the cause of action arose); Bristol-Myers Co. v. Gonzales, 561 S.W.2d 801, 804 (Tex. 1978) (“If a manufacturer knows or should know of potential harm to a user because of the nature of its product, the manufacturer is required to give an adequate warning of such dangers.”); Barrow v. Bristol-Myers Squibb, No. 96-689, 1998 WL 812318, at \*30-31 (M.D. Fla. Oct. 29, 1998) (assessing liability for failure to warn based on what manufacturer knew or should have known at the time the medical device was implanted in plaintiff). Cf. Moore v. Armour Pharm. Co., No.88-392, 1990 WL 369571, at \*4 (M.D. Fla. Aug. 27, 1990) (applying Florida law and holding duty to warn arose at least one year prior to plaintiff’s use of medical product because manufacturer knew or should have known of risk complained of one year prior).

is not excused if it remains purposefully ignorant of a particular risk. The duty to warn is thus a continuing one, and obligates a manufacturer to conduct research and otherwise investigate risks associated with its products,<sup>67</sup> and then update warnings as appropriate.

Consequently, the adequacy of a label can rarely be determined based solely on the face of the label, as GSK would have this Court do.<sup>68</sup> That is particularly so here. These are not cases in which the plaintiffs complain no warning was given,<sup>69</sup> concede the adequacy of the warning for the injury suffered,<sup>70</sup> or fail to argue or present evidence that material risk information was omitted or misstated.<sup>71</sup> Here, the PSC argues that GSK omitted specific and important risk information for patient subpopulations or failed to timely update that information on the label

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<sup>67</sup> Lance, 4 A.3d at 167–68 (“[A manufacturer’s] duty is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge of its products as gained through research, adverse reaction reports, scientific literature, and other available methods.”) (citations and quotations omitted); Baker v. St. Agnes Hosp., 70 A.D.2d 400, 406 (N.Y. App. Div. 1979) (manufacturer has a duty to “keep abreast of knowledge of its products as gained through research, adverse reaction reports, scientific literature and other available methods”); Leibowitz v. Ortho Pharm. Corp., 307 A.2d 449, 434–35 (Pa. Super. Ct. 1973) (“A drug manufacturer may not escape liability by merely ignoring existing reports of side-effects or dangers in the use of its product. Neither may a drug company fail to conduct tests and research to obtain such information. Where the particular case is such that there exists proof that the drug company [was] ignorant of existing facts or derelict in obtaining information readily ascertainable to it, a package insert or label will be considered inadequate, and liability accordingly imposed.”); Texas Pattern Jury Instruction 71.5, comments (“[I]mplicit in the duty to warn . . . is the obligation to keep abreast of scientific knowledge and provide an adequate warning of dangers that were known or should have been known based on the latest knowledge and available information.”).

<sup>68</sup> Tr. 245.

<sup>69</sup> See McNeil, 462 F.3d at 368 (distinguishing Rolen v. Burroughs Wellcome Co., 856 S.W.2d 607 (Tex. App.1993), because it involved allegations that no warning was given and thus mentioning the risk might be adequate, from the case before the court in which plaintiff complained that the warning was inadequate because it understated the risk level).

<sup>70</sup> In re Rezulin Prods. Liab. Litig., 331 F. Supp. 2d 196, 199–200 (S.D.N.Y. 2004) (label adequate as a matter of law where label provided table identifying incidence of side effects complained about and plaintiffs conceded adequacy of those warnings by arguing that the warning of another side effect unrelated to plaintiffs’ injuries was inadequate).

<sup>71</sup> Felix, 540 So. 2d at 104 (label warning of Accutane’s teratogenic effect in animal studies adequate as a matter of law where there was no contention that label contained a misstatement and there was no evidence at time of ingestion of any teratogenicity in human infants).

when it had actual or constructive knowledge of those risks, and ignored or failed to investigate data that put GSK on notice of particular risks.

Moreover, these cases do not involve side effects unrelated to the health effects of the underlying condition for which the drug is indicated where a generalized warning about the risk might suffice. Type 2 diabetics inherently face higher cardiovascular risks; a generalized warning therefore may not alert prescribing physicians of the CHF risks of Avandia, particularly for vulnerable subpopulations.

Thus, mindful of the general rule that adequacy is ordinarily a question for the jury and must be determined based on both risks disclosed and the manufacturer's actual or constructive knowledge at the time the injury occurred, the Court must consider whether the PSC has presented evidence sufficient for a reasonable jury to conclude that known or knowable material risk information was omitted from or misstated in the 2001 and 2007 labels, rendering them either inaccurate, ambiguous, ineffective, or misleading.

By engaging in this inquiry, the Court does not mean to imply that adequacy can never be a question of law. The Court finds only that, in the context of this omnibus motion and given the nature of the allegations of inadequacy, the Court cannot determine adequacy based solely on the face of the 2001 or 2007 labels without evaluating the PSC's evidence of early safety signals and evolving research findings and safety signals regarding specific CHF risks.

**B. The PSC's Evidence of Inadequacy**

**1. *Adequacy of the Warnings Regarding the Relative CHF Risks of Avandia and Actos.***

The PSC argues and presents evidence that GSK: had notice in 2001 that Avandia posed

a greater risk of CHF than the competitor drug Actos; lobbied to obtain a class-wide warning of CHF (that is, a warning that applied to Actos as well as Avandia) despite the FDA's reluctance to do so; purposefully avoided head-to-head trials that might elucidate the comparative risk of Avandia and Actos; and failed to report any greater CHF risk from Avandia until the 2011 label amendment, though it had access to study data that would have permitted it do so as early as 2008. The PSC asserts, therefore, that neither the 2001 label, nor even the 2007 label can be found adequate as a matter of law. Notably, the PSC does not dispute that there is a class-wide CHF risk.<sup>72</sup> Instead, it asserts the class-wide warning, absent disclosure of the purported higher relative risk from Avandia, rendered the label inaccurate and misleading by suggesting an equal level of risk from both drugs in the face of both early signals and later scientific evidence suggesting the contrary.

At the time of or just after adoption of the 2001 revised label, GSK had postmarketing adverse event report ("AER") data suggesting there were significantly more incidents of CHF reported for Avandia users compared to Actos users. In early 2001, just after adoption of the revised label warning that Avandia "like all thiazolidinediones" can cause fluid retention, which may lead to or exacerbate CHF, GSK statistically analyzed AER data both for Avandia and Actos, and found that reported incidents of CHF were twice as high for Avandia than for Actos.<sup>73</sup> Just prior to approval of the 2001 label, the FDA expressed reluctance to characterize CHF as a class-wide issue due to the lack of data regarding Actos and CHF,<sup>74</sup> but the class-wide CHF

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<sup>72</sup> Tr. 231.

<sup>73</sup> PSC Resp., Exs. 18–20.

<sup>74</sup> PSC Resp., Ex. 10 (Jan 30, 2001 draft label revisions including the FDA comment that "The FDA team awaits information regarding [Actos] to evaluate whether CHF is really a class issue").

warning was nonetheless included in the 2001 label warning. The record evidence also shows GSK resisted conducting comparative studies for Avandia and Actos, including those with CHF-related endpoints.<sup>75</sup>

The PSC also argues that neither the 2001 label nor 2007 label reflected observational studies and meta-analyses indicating higher CHF risks from Avandia compared to Actos that were available to GSK as early as 2007. A GSK Advisory Committee discussed a 2007 *Lancet* article that reported results of a meta-analysis of various clinical studies and found a significantly higher incidence of CHF from Avandia compared to Actos (“[Actos] has only ½ of CHF compared with [Avandia]”).<sup>76</sup> Some committee members expressed the need to “get away from” relative risk characterizations.<sup>77</sup> In addition, multiple observational studies and meta-analyses involving both Avandia and Actos were conducted between 2007 and 2010, from which a 2011 study concluded that there was a statistically significant increase in the risk of CHF from Avandia.<sup>78</sup>

Despite the availability of these studies as early as 2007, and evidence that GSK itself had at least a signal about the relative risks in 2001,<sup>79</sup> GSK did not revise the Avandia label to

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<sup>75</sup> PSC Resp., Exs. 17, 69, 70.

<sup>76</sup> PSC Resp., Ex. 74.

<sup>77</sup> PSC Resp., Ex. 74.

<sup>78</sup> PSC Resp., Ex. 75.

<sup>79</sup> GSK argues that the PSC cannot rely on GSK’s 2001 statistical analysis of the AER data because AERs are unreliable spontaneous reports by physicians and other medical professionals and GSK has no duty to report comparative results from AER analysis. GSK Reply at 9; Tr. 183–84. This Court recognizes that other courts have excluded AER data when used for causation purposes, *see, e.g., In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1039–41 (D. Minn. 2007) and *Wade-Greaux v. Whitehall Labs.*, 874 F. Supp. 1441, 1481 (D.V.I. 1994), and the PSC concedes as much, *see* Tr. 204.

include any clinical trial data on relative risks until February 2011, when the revised label included the results from three clinical trials showing a higher risk of CHF hospitalization in elderly patients. GSK itself concedes that the studies included in the 2011 revised label were published “in 2008 or beyond.”<sup>80</sup> Thus, at least some of the results from these trials were available two or more years prior to the 2011 label revision.

Based on this evidence, and because it seems probable that physicians would consider these data on relative risk important in making prescribing decisions, a reasonable jury could conclude that because, at some point after 2001, GSK knew additional studies were warranted regarding relative CHF risk but failed to investigate that risk and had available to it comparative risk information at least as early as 2008, it should have updated the label with comparative risk information<sup>81</sup> at some point after 2001 and before the 2011 label revision.<sup>82</sup> Further, the Court cannot resolve, on this record and as a matter of law, when, precisely, GSK should have known

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The Court need not resolve whether such evidence is admissible for that purpose because the PSC does not offer the AER analysis solely for proof of causation, but instead to indicate notice of a safety signal of the purported higher relative risk, and in the context of GSK’s reluctance to conduct head-to-head trials in light of the AER results. GSK conceded at oral argument that AER data can indicate a safety signal that “may or may not warrant further investigation.” Tr. 180. And the FDA recognizes the value of AER data by requiring that the “Adverse Events” section include spontaneous postmarketing reports of adverse event reports reasonably associated with the drug. 21 C.F.R. § 201.57(c)(7). Postmarketing adverse event reports “provide an opportunity to identify low frequency reactions and reactions not previously observed because the susceptible population was either excluded from the controlled trials or only included in small numbers.” See Final Rule, *supra* note 12, at 3950. Thus, GSK’s analysis of the AER data is relevant and admissible for, at a minimum, demonstrating notice of a potential risk, In re Baycol, 532 F. Supp. at 1042–43, that may have triggered a duty to investigate.

<sup>80</sup> GSK Reply at 8; Tr. 184.

<sup>81</sup> GSK has not conceded that risks of CHF from Avandia are higher than for Actos. But that causation question is not before the court.

<sup>82</sup> The AER data is not, however, sufficient for a jury to determine that the 2001 label was inadequate solely for failure to include the AER comparative data. The FDA does not permit relative risk data in the Adverse Events section of the label without well-controlled studies supporting those comparisons. See supra note 25 and accompanying text.



of the evidence of heightened relative risk and should have updated the label. Accordingly, the Court thus cannot conclude that either the 2001 label or the 2007 label were adequate as a matter of law for patients ingesting Avandia after the label revisions during those years.

**2. Risks for Patients on Sulfonylurea+Avandia Combination Therapy.**

The PSC argues and presents evidence suggesting that GSK knew or should have known that Avandia in combination therapy with sulfonylureas increased CHF risks, yet included misleading statements on the 2001 label and failed to update the label to reflect that risk until at least August 2005. First, the PSC argues that by including in the 2001 label clinical trial results about edema and CHF for only insulin+Avandia combination therapy, GSK implied that combinations with other antidiabetic agents did not implicate CHF risks. The 2001 label's "Adverse Reactions" section included clinical trial results noting higher reports of edema with Avandia monotherapy (4.8%) compared with metformin or sulfonylurea monotherapy. Immediately following that statement, the label asserted that overall adverse experiences with SU+Avandia and metformin+Avandia combination therapies were similar to those with monotherapy. Second, the PSC presents evidence that GSK knew, as early as 2001, that double-blind and open-label studies demonstrated a safety signal for CHF from SU+Avandia combination therapy, and had clinical trial results from overseas studies that demonstrated a greater risk of edema from that combination.<sup>83</sup>

Despite these signals and overseas clinical trial results, GSK did not update the Avandia

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<sup>83</sup> PSC Resp., Exs. 26 ("increased risk of CHF when [Avandia] is initiated at 8 mg in combination with [sulfonylurea]"); 22 (2002 e-mail indicating there may have been a signal of increased risk of CHF with sulfonylurea+Avandia in double-blind studies, and that there was a signal in open-label studies); Ex. 28 (Japanese and other studies showing higher reporting rate for edema in sulfonylurea+Avandia therapy).

label to indicate a significantly higher risk of edema from SU+Avandia therapy (12.4% for SU+Avandia combination therapy compared to 4.8% for monotherapy) until August 2005.<sup>84</sup> Then, in October 2005, GSK released results of a retrospective analysis of 37 existing clinical trials and found an increased risk of CHF from SU+Avandia dual and triple combination therapy.<sup>85</sup> Two months later, the label's Warning was revised to advise that physicians should, in particular, monitor Avandia patients on combination therapy with insulin or sulfonylureas.<sup>86</sup>

Based on this evidence, the Court finds the PSC has presented a genuine issue of material fact as to whether and when, prior to the 2005 label revisions, GSK knew or should have known of study results suggesting patients on SU+Avandia therapy faced a greater risk of edema and should have warned of those risks. Consequently, the Court cannot find, as a matter of law, that the 2001 label's generalized warning that both monotherapy and combination therapy may cause fluid retention, and the generalized advice to monitor all patients was complete, accurate, and unambiguous, if studies then or at some point thereafter indicated some subpopulations faced a heightened risk. Presumably, this information would be important to physicians making prescribing decisions for patients on SU therapy. Moreover, a reasonable jury could find the 2001 label misleading based on the 2001 label's assertion that adverse experiences from combination therapy were similar to those for Avandia monotherapy if studies available after that date suggested or demonstrated a higher risk and GSK failed to update the label to reflect that.

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<sup>84</sup> PSC Resp., Ex. 30.

<sup>85</sup> PSC Resp., Ex. 27.

<sup>86</sup> PSC Resp., Ex. 29.

risk.<sup>87</sup>

### 3. *Risks for Patients with NYHA Class 1 and 2 Stage Heart Failure.*

The PSC argues the Court cannot find the 2001 label adequate as a matter of law, at least as of February 2004, because GSK failed to include available clinical trial results showing an increased risk of edema and CHF for patients with pre-existing NYHA Class 1 and 2 stage heart failure. The PSC also contends that even when the label was revised in 2006 to include those trial results, it excluded data suggesting the risk was even greater than that reported on the label, rendering even the revision inadequate.

At the behest of European regulators, GSK conducted a postmarketing clinical trial to evaluate the safety implications of fluid retention in patients with pre-existing CHF<sup>88</sup>—known as “Study 211.” GSK had the study results at least by February 2004,<sup>89</sup> and in December of that year, submitted the results to the FDA. The trial showed a higher incidence of, *inter alia*, cardiovascular death and hospitalization, worsening or possible worsening of CHF, cardiac failure, new or worsening edema, new or worsening dyspnea, and an increase in CHF medication.<sup>90</sup>

GSK updated the label in 2005 and 2006 to include information about risks to patients with NYHA Class 1 and 2 heart failure. In December 2005, the label was amended to include in

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<sup>87</sup> Cf. Tinnerholm v. Parke-Davis & Co., 285 F. Supp. 432, 452 (S.D.N.Y. 1968) (statement that incidence of reactions from vaccine is usually no greater than those for another vaccine is misleading where the difference was significant, and “any significant increase found to exist in the reaction rate of a particular drug must be disclosed”).

<sup>88</sup> PSC Resp., Exs. 50, 52. In Europe, use of Avandia in patients with pre-existing CHF had been contraindicated for patients with NYHA Class 1–4 status since July 2000. PSC Resp., Ex. 63.

<sup>89</sup> PSC Resp., Ex. 51.

<sup>90</sup> PSC Resp., Ex. 55.

the Warning section a statement that, in addition to monitoring all patients for signs and symptoms of heart failure, doctors should particularly monitor those with NYHA 1 and 2 status.<sup>91</sup> In June 2005, GSK submitted a supplemental new drug application for Avandia tablets and proposed a label revision to include detailed Study 211 results in the Warning's section.<sup>92</sup> The new label was approved in April 2006 and adopted in May 2006.<sup>93</sup>

While the revised label included some of the data associated with CHF-related events, it excluded other data. The label generally reported in the "Warnings" section that "[p]atients with [NYHA 1 and 2] treated with Avandia have an increased risk of cardiovascular events," and that the study included both adjudicated endpoints (based on predefined criteria) and "other cardiovascular adverse events that were reported by investigators." An accompanying table included trial data for CHF-related adjudicated endpoints showing, for example, that 7% of patients on Avandia experienced new or worsening CHF compared to 4% on placebo. The table included investigator-reported, non-adjudicated endpoints for ischemic adverse events, but omitted investigator reports of a significantly higher incidence of cardiac failure (8.8% for control; 17.3% for Avandia) compared to adjudicated CHF-related endpoints. Within GSK, there was some uncertainty about whether the investigator-reported events overestimated, or the adjudicated results underestimated, the CHF risk, yet GSK disclosed only the more favorable data.<sup>94</sup> In 2007, the label was again revised to include a statement that use in patients with

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<sup>91</sup> PSC Resp., Ex. 29.

<sup>92</sup> PSC Resp., Ex. 52.

<sup>93</sup> PSC Resp., Exs. 52, 61.

<sup>94</sup> PSC Resp., Exs. 57 at 17; 58 at 49.

symptomatic heart failure was not recommended.<sup>95</sup>

The PSC contends, and the Court agrees, that the delay in including the Study 211 results creates a genuine factual dispute over the adequacy of the 2001 label, at least from the time at which GSK became aware of the increased risks to Class 1- and 2-status patients and up until the December 2005 revision, which advised doctors were advised to monitor NYHA Class 1 and 2 patients in particular. Though the 2001 label warned that all patients at risk for heart failure should be monitored and, in the less-prominent “Precautions” section, advised that Avandia should be used with caution in patients at risk for heart failure, the Court cannot conclude that this warning is adequate as a matter of law for Class 1 and 2 patients because, by the very nature of Type 2 diabetes, *all* diabetics are at risk of heart failure.<sup>96</sup> A jury could reasonably conclude that the 2001 cautionary language was not sufficiently particularized in the face of studies suggesting certain subpopulations of patients with Type 2 diabetes—those with pre-existing mild, symptomatic heart failure—faced a heightened risk. Moreover, a reasonable jury could conclude that even the revised May 2006 label was misleading because it stated that “other cardiovascular adverse events were reported by investigators,” but included investigator-reported results only for ischemic events and not CHF. A jury could find the exclusion of data on reported CHF events that indicated a two-fold increase in the incidence of CHF misleadingly suggested that no increased incidence of CHF had been observed by investigators.

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<sup>95</sup> PSC Resp., Exs. 65, 71.

<sup>96</sup> GSK’s media materials emphasize this point. PSC Resp., Ex. 25 (GSK January 2002 Final Talking Points) at 4.

#### 4. *Scope and Nature of CHF Risks.*

The PSC argues that the 2001 label was inadequate as to CHF risks because it understated CHF risks generally by: omitting important clinical trial data; only indirectly warning of CHF risks through warnings about fluid retention and edema; and failing to conduct adequate mechanistic studies to elucidate the relationship between Avandia and cardiac hypertrophy. The PSC also argues that GSK watered down the fluid retention warning through its reassuring marketing and media communications.<sup>97</sup>

First, the PSC argues that GSK's inclusion in the Warnings section of the 2001 label of CHF-related clinical trial results for only insulin+Avandia combination therapy trials was misleading because it suggested that only patients using Avandia with insulin were at risk. That the label may have given this impression, despite the general warning that the drug causes fluid retention that can lead to or exacerbate CHF, is supported by the apparent confusion among GSK's own staff, who, in draft talking points for use with the media, initially concluded as

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<sup>97</sup> The PSC also argues that the label was inadequate because, prior to the 2007 boxed warning, information about CHF risks was buried in the bottom half of the label behind information about moiety, pharmacology, pharmacokinetic and drug metabolism, special populations and other information. In support, it offers the deposition testimony of former FDA deputy director of the Division of Drug Risk Evaluation, Dr. Rosemary Johann-Liang. See PSC Resp. at 30–32. GSK argues Johann-Liang's testimony is inadmissible hearsay. The Court need not resolve the admissibility question because it concludes that GSK had no control over the *placement* of the warnings and thus Johann-Liang's testimony does not create a question of fact as to the adequacy of the label. The FDA's regulations mandate the order in which labeling information must appear. See supra Section I.A. But in so concluding, the Court does not suggest that the presentation of risk information within and among the Contraindications, Warnings, Precautions and Adverse Events sections was beyond GSK's control.

Additionally, the PSC argues that because the FDA concluded that a boxed warning was necessary to adequately inform doctors of CHF risks, so, too, could a jury. See PSC Resp. at 47–48. The Court, however, agrees with GSK that, unlike other revisions to augment warnings, a boxed warning can be added only with prior FDA approval. See Ackermann v. Wyeth Pharm., 526 F.3d 203, 211 n.12 (5th Cir. 2008); Schedin v. Ortho-McNeil-Janssen Pharm., No. 08–5743, 2011 WL 834020, at \*4 (D. Minn. Mar. 4, 2011) (assuming without deciding that manufacturer could not have added a boxed warning without prior FDA approval).

much.<sup>98</sup>

Second, the PSC presents evidence that GSK knew that some studies indicated a signal of increased CHF with Avandia monotherapy,<sup>99</sup> and that GSK both failed to include data from early Japanese clinical trials that showed a much higher incidence of edema than GSK's preclinical trials, and attempted to prevent presentation of Japanese results at scientific society meetings in the United States and Europe.<sup>100</sup>

Third, the PSC argues that GSK's pre-approval animal studies demonstrated an association between Avandia and the thickening of heart muscles and fluid retention. Because GSK was aware that those studies had not identified the physiological or toxicological mechanism behind that association, the PSC contends, GSK was on notice that additional studies were needed to explain the association.<sup>101</sup>

Fourth, the PSC argues that the 2001 label's warning that TZDs can cause fluid retention which *may* lead to or exacerbate CHF was insufficient because it was misleading and equivocal as to the direct causal relationship between Avandia and CHF. And evidence demonstrated that GSK's marketing communications sought to dissociate edema from CHF. When the American Diabetes Association and the American Heart Association released a consensus statement that included the conclusion that though the incidence of CHF is very low given the number of

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<sup>98</sup> PSC Resp., Ex. 24 at 4.

<sup>99</sup> PSC Resp., Exs. 22, 23, 24.

<sup>100</sup> PSC Resp., Exs. 28, 31, 32. The 2001 label reported that edema was reported in 4.8 percent of the patients in clinical trials. GSK Mem., Ex. C. In the Japanese clinical trials, edema was observed in 6.3 and 16.8 percent of patients with dosage of 4 mg and 8 mg, respectively. PSC Resp., Ex. 28.

<sup>101</sup> PSC Resp., Exs. 1-5.

patients treated, CHF “may be directly attributable to TZD therapy,”<sup>102</sup> GSK persuaded the ADA/AHA to alter the headline of their press release on the consensus statement to omit the statement that TZDs were linked to heart failure.<sup>103</sup> Further, GSK media talking points and related materials repeatedly emphasized that “implicit in the [Statement] is that edema has multiple causes and does not equate to CHF.”<sup>104</sup> Additionally, when one of GSK’s executives was invited to address the CHF risks at an ADA/AHA meeting prior to its release of the Statement, GSK’s staff urged that the executive dissociate edema and CHF and omit animal data showing cardiac hypertrophy because, among other reasons, it correlates with CHF.<sup>105</sup>

Viewing this evidence<sup>106</sup> in the light most favorable to plaintiffs, the Court cannot conclude, as a matter of law, that the 2001 label’s primary warnings about fluid retention and edema, with a secondary warning for CHF using qualifying language (e.g., “may”) was clear, complete and unambiguous as to the risk of CHF from Avandia for patients prescribed Avandia between 2001 and 2007.<sup>107</sup> A reasonable jury could conclude that the inclusion of only clinical

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<sup>102</sup> PSC Resp., Exs. 40, 77.

<sup>103</sup> PSC Resp., Ex. 42.

<sup>104</sup> PSC Resp., Exs. 42, 46, 47, 48.

<sup>105</sup> PSC Resp., Exs. 38.

<sup>106</sup> GSK contests the admissibility and reliability of testimony by Dr. Suzanne Parisian, the PSC’s expert who opines about the adequacy of the 2001 label. But GSK does not assert that, under the laws of the four states at issue here, the PSC must submit an expert affidavit to survive summary judgment on adequacy. And indeed, it appears requirements for experts vary by state. Compare Dion v. Graduate Hosp. of Univ. of Pa., 520 A.2d 876, 881 (Pa. Super. Ct. 1987) (expert testimony required where the “meaning of the warning eludes the comprehension of an ordinary layperson”) with Upjohn Co. v. MacMurdo, 562 So. 2d 680, 683 (Fla. 1990) (adequacy or inadequacy must, except in more obvious situations, be proved by expert testimony). Instead GSK argues only that GSK need not support *its* motion with expert testimony and that Parisian’s affidavit is insufficient to create a question of fact. Because the Court concludes a reasonable jury could find the 2001 and 2007 labels inadequate without consideration of Parisian’s testimony, it declines to decide, at this juncture, the admissibility of her opinions.

<sup>107</sup> GSK has not stipulated that Avandia causes CHF.



data for insulin combination therapy trials, the exclusion of clinical data showing a higher incidence of edema than that provided in the “Precautions” section of the label, and the only indirect warning regarding CHF rendered the 2001 label inadequate. Further, a reasonable jury in a jurisdiction recognizing an overpromotion exception could conclude that GSK’s efforts to dissociate edema from CHF diluted the effect of the 2001 warning about the relationship between edema and CHF.<sup>108</sup>

### 5. *Conclusion*

GSK has stressed repeatedly that a label need only be adequate, not perfect.<sup>109</sup> The Court does not require a showing of perfection to find a label adequate as a matter of law; instead it requires a finding that no questions of fact remain as to a label’s accuracy, clarity and completeness regarding the scope and nature of the risk in light of what a manufacturer knew or should have known at the time a cause of action arose. The Court cannot make such a finding here. In short, a reasonable jury could conclude that although the 2001 and 2007 labels warned about CHF risks, they did not do so specifically enough or directly enough. Accordingly, the motion for summary judgment must be denied.

This conclusion, however, should not be construed as suggesting that the adequacy of *current* warnings remains in question or that plaintiffs claiming CHF injury from Avandia have

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<sup>108</sup> At least one state—Pennsylvania—has adopted an “overpromotion” exception to the learned-intermediary doctrine under which a drug manufacturer may be held liable for inadequate warnings where marketing representations dilute the warnings of an otherwise adequate label. See Incollingo, 282 A.2d at 220. Where evidence of overpromotion is presented, the question of adequacy is one for the jury. Id. Whether any other state at issue here has a similar exception is unclear. The PSC argued that Texas courts have recognized an overpromotion exception, Tr. 214, but, beyond the exception for off-label promotion, Tex. Civ. Prac. & Rem. § 82.007(b)(3), the Court was unable to identify any general overpromotion exception. See Ebel v. Eli Lilly and Co., 536 F. Supp. 2d 767, 781 (S.D. Tex. 2008) (declining to predict whether Texas would adopt the exception of overpromotion to the learned intermediary doctrine).

<sup>109</sup> Tr. 246, 247, 251.

an easy litigation road ahead of them. First, though the Court concludes that it can find neither the 2001 nor 2007 label adequate as a matter of law, it seriously questions whether any plaintiff claiming CHF injury after access to Avandia was restricted in September 2010, much less after the 2011 label revision, can succeed on a failure to warn theory. Second, adequacy of the label, not causation, was at issue in this motion. Whether individual plaintiffs can show specific causation as medical practitioners' knowledge of CHF risks from Avandia grew, is an entirely different question.

#### **IV. DISCOVERY**

The PSC requests additional discovery targeted at CHF risks, asserting that discovery has focused largely on myocardial infarction ("MI") and that additional discovery is required as to GSK's knowledge of CHF risks in preclinical studies, GSK's knowledge of relative CHF risks, the development of and negotiations surrounding the 2001 and subsequent labels, and GSK's marketing activities. In addition, the PSC seeks additional expert discovery, contending that the Parties agreed to limit PSC expert reports to MI issues, as well as additional depositions. GSK opposes the request, arguing that the PSC has had ample opportunity to conduct CHF-related discovery; that GSK has produced more than eight million pages of documents regarding CHF; and that there was no agreement to limit discovery or expert reports to MI matters.

Because the Court finds summary judgment inappropriate based on discovery to date, it declines to consider the PSC's request, in the alternative, for additional discovery. The Court will consider, however, any properly filed motion for additional discovery specific to CHF risks.

#### **V. CONCLUSION**

For the foregoing reasons, the Court will deny GSK's motion for summary judgment. An appropriate Order follows.