

# Section Connection



## Toxic, Environmental & Pharmaceutical Torts (STEP)

Where Resources Come Together

A Publication of the American Association for Justice formerly Association of Trial Lawyers of America (ATLA®)

Vol. 15, No. 1, Fall 2007

### INSIDE

Page 4  
AAJ  
Regulatory  
Update

Page 5  
Gadolinium-  
based MRI  
Contrast Dye  
and its Causal  
Link to  
Nephrogenic  
Systemic  
Fibrosis

Page 10  
AAJ  
Exchange  
Litigation  
Packet  
Preview

Back Issues of  
Section on Toxic,  
Environmental &  
Pharmaceutical  
Torts (STEP)  
newsletters can  
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## New Litigation for Off-Label Use of Drug-Eluting Stents

By Stacy K. Hauer and Ronald S. Goldser, Minneapolis, Minn.

Manufacturers first produced drug-eluting stents (DES) in 2003. Unfortunately, DES are associated with an increased risk of serious and often fatal complications when used for purposes beyond those



Stacy K. Hauer

approved by the FDA (off-label use). Patients implanted with DES are at an increased risk for late stent thrombosis which can lead to serious heart attacks.

### WHAT IS A STENT?

A stent is a tiny, metal mesh tube used to prop open clogged coronary arteries. Stents are generally implanted via a balloon catheter that is inserted into the femoral artery and guided into the arteries of the heart. The balloon is then inflated to dilate the artery, and the stent is expanded.

Once expanded, the stent creates a scaffold that opens blockages in the artery and prevents the artery from collapsing or becoming blocked again. Stents have become very popular with patients and cardiologists because the procedure is not nearly as invasive as traditional bypass surgery and does not require an extended hospitalization.

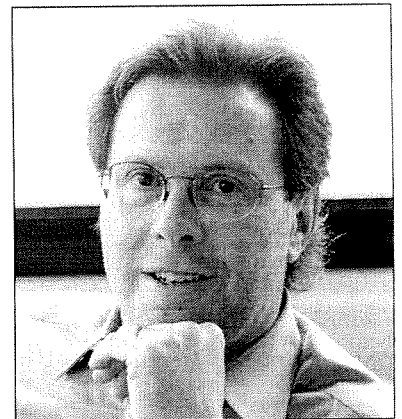
### BARE METAL STENTS VERSUS DRUG-ELUTING STENTS

The first stents, introduced in 1994 as bare metal stents, were wire-mesh medical devices made typically of stainless steel with no drug or other coating on the metal. Cardiologists viewed bare metal stents as a significant innovation, and their use soared. A number of manufacturers produce models that are used in the United States.

Unfortunately, scar tissue formed within the stent in a certain percentage of people. The scar tissue resulted in the narrowing of the arteries, a process called in-stent restenosis. In-stent restenosis could lead to the artery becoming blocked again.

Because of the danger posed by in-stent restenosis, medical device manufacturers ultimately began to produce DES. DES are simply bare metal stents coated

with a polymer containing a drug intended to reduce the risk of in-stent restenosis. The drug coated stent is designed to prevent the formation of scar tissue as the artery heals and a thin layer of endothelial cells forms



Ronald S. Goldser

over the stent. This layer of endothelial cells, once formed, prevents blood clots, or thrombosis, within the stent.

Since 2003, DES have become some of the best selling, most profitable products in the medical device business. Up until 2006, DES were inserted into the arteries of a million people per year and generated about five billion dollars a year in sales.<sup>1</sup> However, recent reports indicate that DES sales have fallen by

*continued on Page 2*

*Drug-Eluting Stents cont. from Page 1*

nearly one-third over the last 12 months.<sup>2</sup>

Two DES models are currently on the market. Cordis Corporation, a subsidiary of Johnson & Johnson, makes the CYPHER® stent. The CYPHER® stent is coated with a polymer that slowly emits a drug called sirolimus.<sup>3</sup> Boston Scientific manufactures the TAXUS® stent which is coated with the drug paclitaxel<sup>4</sup> and which works like the CYPHER® stent.

Patients who received these stents were instructed to be on anti-platelet therapy for three to six months to prevent thrombosis. The anti-platelet therapy includes the use of aspirin or clopidogrel (Plavix) to prevent blood clots. Recent recommendations from the FDA are for six to twelve months of anti-platelet therapy.<sup>5</sup>

**OFF LABEL USE**

DES were approved by the FDA for very limited purposes. However, use of these stents for off-label purposes has soared. Off-label use of DES is pervasive;

it has been reported that at least 60 percent of DES are used in off-label situations.<sup>6</sup> Some of the most common off-label use situations include diabetic patients, patients who are suffering from an acute myocardial infarction, and patients implanted with more than two stents. According to recent reports, patients who received a DES for an off-label purpose are at a greater risk of late stent thrombosis.<sup>7</sup>

**PROBLEMS WITH DRUG-ELUTING STENTS**

DES are associated with late stent thrombosis, which is a clot that occurs in the stent more than 30 days after it is placed in the artery. A clot in the stent obstructs blood flow and can lead to an acute myocardial infarction (MI), more commonly known as a heart attack. A thrombosis of this type is fatal in over one-third of cases.

While clots also occur in stents within the first 30 days after implant (sub-acute thrombosis), DES cause no greater risk

*continued on Page 3*

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*Drug-Eluting Stents cont. from Page 2*

than bare metal stents during this time period.

By preventing in-stent restenosis, DES prevent the interior wall of the coronary artery from re-endothelializing, or healing over. Until the interior coronary artery wall heals over, a patient is at a much greater risk for MI.

Recent studies have shown that DES cause delayed healing, resulting in the thin endothelial layer of cells forming unevenly, if at all, thereby requiring much longer use of anti-platelet therapy than originally recommended. A recent study found that DES showed delayed healing – causing the thin endothelial layer of cells that would normally cover the metallic stent to be uneven or non-existent.<sup>8</sup> Another study demonstrated that bare metal stents have greater endothelialization than DES.<sup>9</sup> Thus, it appears that either the failure to heal or the delay in healing contributes to late stent thrombosis.

There has also been a number of meta-analysis or statistical studies looking at late stent thrombosis associated with DES. In 2006, one of the first statistical analysis of DES showed a two-fold increase in thrombosis-related events 12 months after discontinuation of anti-platelet therapy.<sup>10</sup>

This report was followed by another meta-analysis that found the incidence of death and heart attack was higher in patients who received DES.<sup>11</sup> The study concluded that the increase was due to late stent thrombosis. Following this presentation, one of the manufacturers admitted it had data to support these conclusions.<sup>12</sup>

At the recently held 2007 European Society of Cardiology Annual Meeting, dozens of presentations and abstracts comparing bare metal stents and DES were presented. Data presented by Dr. Gabriel Steg found that the Global Registry of Acute Coronary Events (GRACE) showed a higher rate of mortality in MI patients with DES than with traditional bare metal stents.<sup>13</sup>

**FDA PANEL**

On September 14, 2006, the FDA

issued a statement regarding the risk of late stent thrombosis and DES. The FDA convened a panel of cardiologists to address the safety of DES on December 7-8, 2006.<sup>14</sup> The purposes of this meeting were: (1) to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis (both when DES are used according to their label and in more complex off-label situations), and (2) to address the appropriate duration of anti-platelet therapy (aspirin plus clopidogrel) in patients receiving DES.

The Panel determined that both the CYPHER® and the TAXUS® stents are associated with a greater risk of late stent thrombosis compared to bare metal stents when used according to the label, but that the benefits appear to outweigh the risks. The Panel also determined that larger and longer pre-market clinical trials and a longer follow-up period for post-approval studies were needed.

However, with respect to off-label uses of DES, the Panel agreed that off-label use is associated with an increased risk of late stent thrombosis, MI, and death compared to on-label use. Further, the Panel concluded that additional studies are needed to determine optimal treatments for more complex patients. In addition, the Panel decided that DES labels should state that when DES are used off-label, patient outcomes may not be the same as the results observed in the clinical trials.

**LITIGATION**

Patients who received a DES and later suffered from late stent thrombosis have already filed several lawsuits. The company headquarters for Cordis, who manufactures the CYPHER® stent, is located in Florida, and lawsuits have been filed in at least two Florida state courts.

The TAXUS® stent is manufactured by Boston Scientific, and lawsuits relating to this device have been filed in Massachusetts state courts. A multi-district litigation petition has not been filed because the cases have only been filed in state court.

*Liability Theories*

Liability theories thus far are based in strict products liability, including failure to warn, failure to test, and negligence. For example, a review of the CYPHER® materials provided to physicians carried no warning about clotting at the stent site.

Further, the manufacturers' advertising materials and the press releases which promoted off-label use and provided misleading information about clinical testing could support a fraud theory. The information provided about the superiority of DES may not be accurate because the clinical trials used a very narrow patient profile that does not match up with real world practice. For example, the bare metal stents used in clinical trials were vastly different in thickness than those used in clinical practice. Thus, the benefit of DES may have been inflated as a result of the design of the trials.

*Defenses*

The first question in a medical device case is: what about preemption? CYPHER® cases have been filed in Florida. While there is not a Florida state case precisely on point, there is an 11th Circuit case from Florida in plaintiff's favor ruling against preemption of state law claims.<sup>15</sup> Similarly, in Massachusetts, where TAXUS® cases have been filed, there is a decision in state court ruling against preemption of state law claims.<sup>16</sup>

However, the pre-emption issue in the medical device context is currently before the United States Supreme Court.<sup>17</sup> In addition, the Senate Judiciary Committee is currently holding hearings on this issue. Regardless of the outcome of these proceedings, the pre-emption defense most likely will fail because such a large percentage of DES usage is off-label and no warnings or FDA approved label existed for the off-label use.

Defendants will likely attack each case on case specific causation as well. Admittedly, these plaintiffs are people who have a history of cardiovascular issues. However, an expert may be able to look at diagnostic tests such as a heart

*continued on Page 4*

*Drug-Eluting Stents cont. from Page 3*

catheterization or an angiogram and see the clot at the stent site and be able to provide causation opinions.

These cases have only recently been filed, and discovery is in its early stages. The liability theories and defenses that arise in these cases will likely evolve as the litigation develops.

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1. Mark Jewell, *Safety Questions Expected to Take \$1 Billion Bite Out of U.S. Stent Market*, Associated Press, [http://biz.yahoo.com/ap/070816/stent\\_struggles.html?\\_v=1](http://biz.yahoo.com/ap/070816/stent_struggles.html?_v=1) (Thursday, August 16, 2007).
2. *Id.*
3. Sirolimus is an antibiotic drug better known as rapamycin.
4. Paclitaxel is a chemotherapeutic drug better known as Taxol.
5. See Update to FDA Statement on Coronary Drug-Eluting Stents, <http://www.fda.gov/cdrh/news/010407.html> (January 4, 2007).
6. *Id.*
7. Hrut K Win, MD, MRCP et al., *Clinical Outcomes*

- and *Stent Thrombosis Following Off-Label Use of Drug-Eluting Stents*, 297 JAMA, 2001, 2001-09, <http://jama.ama-assn.org/cgi/reprint/297/18/2001.pdf> (May 9, 2007).
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  9. Guagliumi G. et al., *Drug-Eluting Versus Bare Metal Coronary Stents: Long-Term Human Pathology*, 4(10) Ital. Heart J. 713, 713-20 (2003).
  10. Mattias Pfisterer, MD, FACC et al., *Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluted Stents*, 48, J. Am. College of Cardiology 2584-91 (Nov. 2, 2006).
  11. Alain J. Nordmann et. al., *Safety of Drug-Eluting Stents: Insights from a Meta-Analysis*, <http://www.escardio.org/NR/rdonlyres/702758E8-7659-4DD8-B67B-611349F32AAB/0/707010NordmannSLIDES.pdf> (September 3, 2006).
  12. Sylvia Pagan Westphal & Ron Winslow, *Boston Scientific Acknowledges Risks Tied to Stent*, Wall St. J., <http://online.wsj.com/article/SB115759122980255909.html> (subscription required) (Sept. 7, 2006).
  13. P.G. Steg, *Increased All-Cause Mortality at 2 Year Follow-Up After PCI With DES vs Bare Metal Stents in Acute Coronary Syndromes: the GRACE Registry Experience*, Hotline III #3218, World Congress of

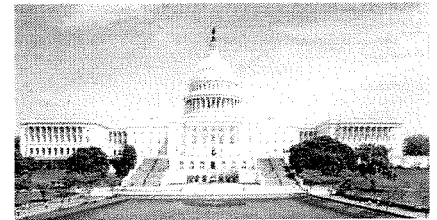
Cardiology Meeting, Vienna, Austria, abstract available at <http://www.escardio.org/vpo/Press+Area/2007-esc-congress-pr/DES-MI-Steg.htm> (September 4, 2007); *News From the Congress: Drug eluting stents – the controversy continues*, European Society of Cardiology, [http://www.escardio.org/congresses/esc\\_congress/esc2007/news/GRACE-steg.htm?hit=esc07](http://www.escardio.org/congresses/esc_congress/esc2007/news/GRACE-steg.htm?hit=esc07); see also Cardiology Today, GRACE: *Drug-eluting stents should be used with caution in patients with STEMI*, <http://www.cardiologytoday.com/200710/grace.asp> (October 2007) (noting that survival rates between six months and two years show a statistically significant difference – 8.6 percent of patients receiving DES had died and 1.6 percent of patients receiving bare metal stents had died).

14. Update to FDA Statement on Coronary Drug-Eluting Stents, *supra* n. 5.
15. *Goodlin v. Medtronic, Inc.*, 167 F.3d 1367 (11th Cir. 1999).
16. *Brown v. DePuy Spine, Inc.*, 2007 WL 1089337 (Mass. Super. April 9, 2007).
17. *Riegel v. Medtronic, Inc.*, 451 F.3d 104 (2d Cir. 2006), *cert. granted*, 127 S.Ct. 575 (2006).

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## Congress Takes Notice of Federal Agencies' Preemption Attempts

### *An AAJ Regulatory Update by Gerie Voss*



Through the Regulatory Advocacy Program, AAJ has taken additional steps to fight back against federal agency attempts to preempt state tort law through the regulatory process. AAJ has continued to educate Congressional staffers on what appears to be a Bush Administration effort to include language seeking to preempt state tort law in the preambles to several different agency rules.

As a result, Democratic Senator Patrick Leahy of Vermont called a full Judiciary Committee hearing for September 12, 2007 titled "Regulatory Preemption: Are Federal Agencies Usurping Congressional and State Authority?" The hearing consisted of four witnesses, including AAJ member Collyn Peddie.

The hearing explored several different areas in which federal agencies have attempted to preempt state tort law through the use of preemption language in the preambles to agency rules including prescription drugs, motor vehicle liability, railroad derailments, and chemical facility

security. We hope this hearing draws attention to this escalating problem and encourages congressional members to pass legislation that will prevent federal agencies from further seeking to subvert the legislative process.

AAJ will also file comments in response to the Food and Drug Administration's (FDA) recently proposed rule regarding labeling of sunscreen products. In this proposed rule, the FDA sought to amend the current requirements regarding both UVA and UVB rays, testing, directions for application, and other indications.

In the federalism section of the proposed rule, the FDA indicates that the rule would have a preemptive effect on state law. The FDA finds that express preemption of state law pursuant to Section 751(a) of the Federal Food, Drug, and Cosmetic Act exists, and it operates to preempt states from imposing requirements related to the regulation of nonprescription drugs.

In addition, the FDA claims that any

final rule would preclude states from issuing requirements related to the labeling and testing of sunscreen products that are different from or in addition to the requirements in the final rule. The FDA claims that not only does Section 751(a) act to preempt both state legislative requirements and common law duties, but it also believes that implied preemption may operate to preempt state tort law pursuant to *Geier v. American Honda Motor Co. Inc.*, 529 U.S. 861 (2000).

Accordingly, any consumer who utilizes a particular sunscreen for a lengthy time period and sustains injuries or illnesses, such as skin cancer, would be unable to hold the manufacturer accountable if the product was defective. AAJ will file comments in this proceeding on November 26, 2007.

*If you have any questions regarding these or other regulatory issues, please contact Gerie Voss, AAJ's Regulatory Counsel, at (202) 965-3500 ext. 748 or at [gerie.voss@justice.org](mailto:gerie.voss@justice.org).*

# Gadolinium-based MRI Contrast Dye and its Causal Link to Nephrogenic Systemic Fibrosis

By Lauren M. DeLong, Cincinnati, Ohio and Jeffrey D. Pederson, Englewood, Colo.

**N**ephrogenic Systemic Fibrosis (NSF), a disease first observed less than a decade ago, is now generally considered by the scientific and medical community to be a man-made, full-scale systemic disorder promising pain and limited mobility to those afflicted with it and threatening to culminate in sys-



**Lauren M. DeLong**

temic failure and death. Many victims slowly and painfully lose control of their extremities until they are frozen in place as the soft tissue of their muscles and tendons gradually becomes fibrotic.

One sufferer described NSF as being similar to "Lou Gehrig's disease, but with severe pain." Ultimately, many succumb to NSF when the disease causes internal organs, such as the heart, to become fibrotic.

As researchers struggle with limited resources to understand NSF, those whose lives it has affected attempt to face the harsh reality of their progressive, physical decline as the result of undergoing an injection of gadolinium-based contrast dye, usually for magnetic resonance imaging (MRI). The victims believed that the MRI would be a

completely innocuous diagnostic procedure.

In 2000, researchers published the first documentation of NSF, known then as Scleromyxoedema-like cutaneous disease, and later changed to Nephrogenic Fibrosing Dermopathy. They identified a disease characterized by extensive thickening, hardening, and discoloration of the patient's skin, most commonly on the arms and legs, dermatological lesions and nodules, and, occasionally, contracture of the joints.<sup>1</sup> The researchers noted that each of the 15 patients from the early case series was on dialysis for varying degrees of renal insufficiency.

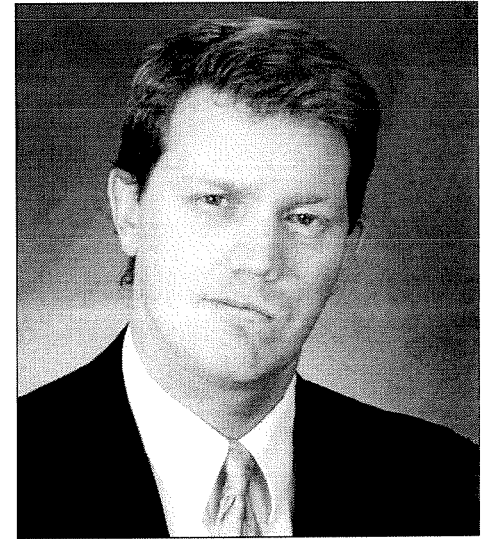
In 2001, Shawn Cowper of Yale University published a report, noting that "[t]he recent emergence of this condition and the apparent clustering of cases in specific dialysis centers initially suggested a possible infectious and/or toxic agent. To date, however, no such agent has been identified."<sup>2</sup>

As the NSF reports grew, researchers gradually became suspicious that the cause of NSF may be exposure to gadolinium-containing contrast dyes used in MRI and magnetic resonance angiography (MRA) procedures. The free gadolinium ion ( $Gd^{3+}$ ) is a highly-toxic, heavy metal toxin. Because gadolinium is not only toxic, but also unknown to the human body, it must be paired with an organic chelating agent before it can safely be used within the human body.<sup>3</sup>

The chelate, which forms a protective coating around the gadolinium metal, is needed to prevent the gadolinium from interacting with the body tissue and to allow the excretion of the gadolinium.<sup>4</sup> If successfully and safely contained, gadolinium administration in connection with MRI and MRA procedures provides physicians and radiologists with an improved diagnostic

tool; however, when its administration is unsuccessful and unsafe, the risks are dire.

The bond that connects the gadolinium to the chelate over time will reject the gadolinium for other metals in the blood stream that have a stronger potential bond to the chelate. These



**Jeffrey D. Pederson**

metals can include zinc, copper, calcium, and some types of iron. This transmetallation then allows the gadolinium to float free in the blood system.

The propensity for transmetallation of the contrast dye chelate is the reason NSF only strikes those already suffering from renal failure. While gadolinium-containing contrast agents are largely excreted within a period of approximately 90 minutes in a patient with normal kidney function, the gadolinium-based contrast agent can remain in the body of someone with renal failure for a period of 30 hours or longer.<sup>5</sup> The longer the period the dye is circulating in the blood stream, the greater the chance that the chelate will dissociate

*continued on Page 6*

*MRI Contrast Dye cont. from Page 5*

from the gadolinium and attach to another metal in the blood stream and cause the gadolinium to float free. Once free, the highly toxic gadolinium may initiate the process leading to NSF.<sup>6</sup>

Indeed, free gadolinium can be both detected and quantified in the tissue of patients who have been diagnosed with NSF, and it is the presence of gadolinium from the contrast dye that is the fingerprint left at the scene of the crime. After researching and publishing on the detection of gadolinium in four tissue specimens, a number of physicians, including Dr. Whitney High and Dr. Shawn Cowper, published a letter to the editor in 2006 documenting their use of a form of mass spectrometry to determine that the average level of gadolinium in lesional skin of a patient with NSF was 70 ppm.<sup>7</sup>

This number is remarkable because there is no normal amount, also known as background rate, of gadolinium that is expected to exist in the human body. As gadolinium is not normally found within the human body, it enters the body only through the administration of a gadolinium-containing contrast dye. Even General Electric (GE), the maker of Omniscan, the dye that owns the largest share of the gadolinium-based contrast dye market, has arguably conceded a causal link between gadolinium-based contrast dye and the onset of NSF.<sup>8</sup>

While GE holds the largest market share, three other entities control the remaining portion of the market for gadolinium-based contrast dye. The Food and Drug Administration (FDA) approved Bayer Health Care's Magnevist in 1988, Bracco Diagnostics's ProHance and MultiHance in 1992 and 2004, respectively, and Tyco Health Care's OptiMARK in 1999. The primary difference between these manufacturers is that each dye has a distinctive molecular combination to chelate the gadolinium.

The different chelates have led to differing rates of NSF. Studies have indicated that the macrocyclic chelates in

ProHance and MultiHance are safer because the gadolinium is wrapped in a ringed chelate that is less likely to disassociate. The linear structures of Magnevist, Omniscan, and OptiMARK provide for a greater likelihood of disassociation. Moreover, because gadolinium is a positively charged element,

generally accepted in the mainstream radiology, nephrology, dermatology, and pathology/dermatopathology communities that a causal relationship exists between exposure to a gadolinium-based contrast agent and NSF, *provided* that moderate to severe renal insufficiency existed prior to exposure.

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**“...it is the presence of gadolinium  
from the contrast dye that is the  
fingerprint left at the scene of the crime.”**

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chelates with a negative charge, like those found in Magnevist and MultiHance, bind more effectively to the gadolinium than chelates without a charge, like those found in Omniscan, OptiMARK, and ProHance.

Suspicious that gadolinium may lead to the development of NSF caused GE Healthcare to release a Dear Healthcare Professional letter on June 6, 2006. The letter acknowledged 25 cases of NSF in the preceding four years. Following the letter, the FDA posted a notification on its Web site on June 8, 2006 reporting on “a possible link between NSF/NFD and exposure to gadolinium containing contrast agents used at high doses for a procedure called Magnetic Resonance Angiography (MRA).”

Of note, none of the five gadolinium-containing contrast dyes have been approved for use in MRA procedures, where up to three times the dose of contrast dye is administered as compared to an MRI. After more articles connecting the development of NSF to gadolinium-containing contrast dyes appeared in the medical and scientific literature, the FDA increased their warnings on December 22, 2006. In March of 2007, GE Healthcare published a paper on NSF on its Web site.<sup>9</sup> Finally, on May 23, 2007, the FDA requested a black-boxed warning.<sup>10</sup>

These cases will involve enormous damage claims, and the manufacturers can be expected to mount a vigorous defense of their product. However, it is

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**Notes:**

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8. *GE Healthcare Paper on Nephrogenic Systemic Fibrosis*, [http://www.ctisus.org/GE\\_White\\_paper\\_on\\_NSF.pdf](http://www.ctisus.org/GE_White_paper_on_NSF.pdf) (March 2007).
9. *Id.*
10. FDA News, *FDA Requests Boxed Warning for Contrast Agents Used to Improve MRI Images*, <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01638.html> (May 23, 2007).

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# Avandia Litigation

## *An AAJ Exchange Litigation Packet Preview*

Avandia, manufactured by GlaxoSmithKline, is prescribed to treat type II diabetes. Type II diabetes results from insulin resistance, a condition in which the body fails to properly use insulin, combined with relative insulin deficiency.<sup>1</sup> According to the U.S. Food and Drug Administration (FDA), between 18 and 20 million Americans suffer from type II diabetes.<sup>2</sup>

Generally five classes of treatment exist for type II diabetes, one of which is the thiazolidinediones class of medications, including Avandia, Rezulin, and Actos.<sup>3</sup> The thiazolidinediones class of diabetes drugs lowers a patient's blood sugar, increasing their sensitivity to their own insulin, rather than increasing the production of insulin or reducing glucose uptake like the other classes.<sup>4</sup>

After the Rezulin recall in 2000, half a million type II diabetes patients were left searching for a new medication. Two other drugs in the same thiazolidinediones family, Avandia and Actos, were kept on the market and marketed as safer alternatives.<sup>5</sup> Avandia quickly became the top seller. Currently, Avandia is GlaxoSmithKline's second best selling drug and has generated sales of three billion dollars in 2006.<sup>6</sup>

On May 25, 1999, the FDA approved Avandia for treatment of type II diabetes. At the time of the FDA's approval, the agency's primary medical reviewer expressed concerns about a potential "deleterious long-term effect on the heart" and recommended a post-marketing study to investigate these concerns.<sup>7</sup>

On May 21, 2007, a meta-analysis of 43 previous studies was published by the New England Journal of Medicine. The new study, conducted by Dr. Steven Nissen and his colleague Kathy Wolski, analyzed data from 43 studies involving 15,560 patients who took Avandia and 12,283 patients who were given other medications or a placebo.<sup>8</sup>

The study reported that patients taking Avandia were 43 percent more likely to have a heart attack and 64 percent more likely to die from cardiovascular causes.<sup>9</sup>

In response to the new study published by the New England Journal of Medicine, GlaxoSmithKline issued a press release pointing to the limited nature of the study and adding that it had initiated the most comprehensive and rigorous program of scientific analysis for any oral anti-diabetic medicine on the market today.<sup>10</sup>

On the same day that the article became available, the FDA issued a safety alert for Avandia. The labeling change will include a new warning about the potential increased risk of heart attack and chest pain observed in some patients treated with Avandia.<sup>11</sup> Since Avandia's approval, the FDA has updated the drug's labeling several times to provide information about its potential associated risk of other adverse heart-related events (congestive heart failure, fluid retention, and edema, among others).

On June 6, 2007, legislators addressed the Avandia issue at a House Oversight and Government Reform Committee hearing. Committee members questioned FDA officials, GlaxoSmithKline representatives, and independent researchers in a four hour session that centered discussion on the FDA's handling of drug safety and post-market responsibilities.<sup>12</sup> The Committee examined the FDA's failure to obtain an adequate post-market clinical trial to assess the risks of heart attack associated with taking Avandia.<sup>13</sup>

At the hearing, the FDA asked GlaxoSmithKline to put a Black Box warning (highest level of warning) on the Avandia packaging regarding potential increased risk of heart attack and heart disease for those taking the drug.<sup>14</sup> Subsequently, on June 7, the FDA issued a Black Box warning to Avandia that it may cause heart attacks

or cardiovascular problems.<sup>15</sup>

An FDA advisory panel of experts met on July 30, 2007 to study Avandia's safety and help the FDA develop plans for publicizing risks and benefits of the products it regulates.<sup>16</sup> The panel of outside experts recommended to the FDA that Avandia should be kept on the market, despite concern over its heart risks.<sup>17</sup>

Though 20 of the 23 panelists agreed that the use of the drug increased heart risks for those with diabetes, 22 out of 23 said that the balance between the drug's benefits and risks supported its continued use in the U.S.<sup>18</sup> Nearly all of the panelists did agree that the drug's black box warning label should be strengthened to reflect its potential risks.<sup>19</sup> Avandia may have caused 30,000 to 140,000 heart attacks and deaths since it was introduced in the U.S. in 1999, said David Graham, an FDA scientist, at the meeting of agency advisors.<sup>20</sup>

To date, numerous suits have been filed against GlaxoSmithKline over Avandia and its link to an increased risk of heart attack. The claims filed against GlaxoSmithKline have included negligent and reckless failure to warn the general public of the risks associated with taking Avandia, product liability, marketing of a defective drug, failure to provide adequate warnings, fraud, negligence, misrepresentation, expressed warranty for goods, warranty of merchant ability, warranty of fitness, unjust enrichment, and wrongful death.<sup>21</sup>

To give AAJ members an overview of the emerging issues in this litigation and assist them in assessing an Avandia case, AAJ has created this Litigation Packet, which includes:

- Overview of Avandia and the emerging litigation concerning its link to heart attacks and cardiovascular problems
- Sample Avandia Complaint

*continued on Page 8*

*Avandia Litigation cont. from Page 7*

- Sample client intake documents and questionnaires
- Contact information for members who have tried or investigated similar matters
- AAJ Education and *Law Reporter* articles
- News articles and medical journals survey
- Testimony from the June 6, 2007 Congressional Hearing on Avandia
- FDA and NIH articles
- Internet resources, including public and private Web sites

Notes:

1. [www.diabetes.org/about-diabetes.jsp](http://www.diabetes.org/about-diabetes.jsp).
2. *Hearing on FDA's Role in Evaluating Safety of Avandia*, <http://oversight.house.gov> (June 6, 2007).
3. Gale D. Pearson, *The Risk of Congestive Heart Failure Associated With the Use of Avandia and Insulin in Combination Therapy for the Treatment of Type II Diabetes, and the Liability of the Manufacturing Company: GlaxoSmithKline For Not Disclosing the Risks*, AAJ Education Paper.
4. *Id.*
5. *Avandia Litigation*, [www.onlinelawyersource.com](http://www.onlinelawyersource.com).
6. Michelle Fay Cortez, *Glaxo's Avandia May Raise Heart Attack, Death Risks (Update 7)*, Bloomberg News at [www.bloomberg.com](http://www.bloomberg.com) (May 21, 2007).
7. *Hearing on FDA's Role in Evaluating Safety of Avandia*, <http://oversight.house.gov> (June 6, 2007).
8. Kim Dixon, *Glaxo's Avandia Stirs Debate at Diabetes Meeting*, Reuters, <http://uk.reuters.com> (June 26, 2007).
9. *Id.*
10. Maria Esposito, *Avandia: Getting the Facts*, Fox News, [www.foxnews.com](http://www.foxnews.com) (May 22, 2007).
11. *Avandia Safety Alert*, [www.onlinelawyersource.com](http://www.onlinelawyersource.com) (May 22, 2007). For the press release see [www.avandia.com](http://www.avandia.com).
12. Stephen Spotswood, *Congress Debates Avandia's Safety, Researchers' Motives and FDA Role*, U.S. Medicine Information Central, [www.usmedicine.com](http://www.usmedicine.com) (June 26, 2007).
13. *Hearing on FDA's Role in Evaluating Safety of Avandia*, <http://oversight.house.gov> (June 6, 2007).
14. Brenda Frohloff, *Part 2: Avandia, the FDA and the Consumer: First Lawsuit Filed*, [www.lawyersandsettlements.com](http://www.lawyersandsettlements.com) (Jun 25, 2007).
15. Jane Mundy, *Avandia Black Box Warning Comes Too Late*, [www.lawyersandsettlements.com](http://www.lawyersandsettlements.com) (June 13, 2007).
16. *FDA Seeks to Improve Communication with Public about Product Risks*, Insurance Journal, [www.insurancejournal.com](http://www.insurancejournal.com) (June 7, 2007).
17. Joseph Brownstein and Dan Childs, *FDA Panel: Avandia Should Remain on Market*, ABC News, [www.abnnews.com](http://www.abnnews.com) (July 30, 2007).
18. *Id.* This is not a binding vote, but is taken as a suggestion to FDA regulators.
19. *Id.*
20. Justin Blum and Michelle Fay Cortez, *Glaxo's Avandia Should be Pulled, U.S. Scientist Says (Update 6)*, Bloomberg News, [www.bloomberg.com](http://www.bloomberg.com) (July 30, 2007).
21. David Yates, *Avandia Lawsuit Filed in Federal Court*, Southeast Texas Record, [www.setexasrecord.com](http://www.setexasrecord.com) (June 21, 2007). The two most notable suits filed recently are *Dabon v. GlaxoSmithKline, Inc.* in Louisiana and *Stanford v. GlaxoSmithKline Inc.* filed in Texas. See also *Glaxo Sued Over Avandia*, Andrews Pharmaceutical Litigation Reporter (June 21, 2007) and *Part 2: Avandia, the FDA and the Consumer: First Lawsuit Filed*, [www.lawyersandsettlements.com](http://www.lawyersandsettlements.com) (June 25, 2007).

*This article is an excerpt from an AAJ Exchange Litigation Packet, Avandia UPDATED August 2007; 239 pages. Working closely with AAJ members, the Exchange develops Litigation Packets, which contain comprehensive, practical material on "hot" litigation topics and trial advocacy issues.*

*For a detailed Table of Contents, log onto the Exchange at [www.justice.org/exchange](http://www.justice.org/exchange) and click on "Litigation Packets." select "Products" and "View" a packet description, along with the "Table of Contents." Or call the Exchange at (800) 344-3023.*



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