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Defeating The FDA Defense In Rezulin Cases

Dr. John Gueriguian: Hero Or Buffoon?

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Commentary

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Dr. John Gueriguian: Hero Or Buffoon?

By
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and
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[Editor's Note: Zoe Littlepage of Littlepage & Associates in Houston only represents people injured by defective medical products and drugs. She currently handles cases nationally including PPA, Sulzer hip implants, Fen-Phen/Redux, Duract, Trovan, Propulsid and Rezulin. She graduated from Rice University and completed her law degree at the University of Houston Law School. Rainey Booth of Levin, Papantonio in Pensacola, Fla., limits his practice to mass tort litigation focusing on pharmaceutical cases. He received his B.A. from Washington & Lee University and his J.D. from the University of Florida. This is part two of a three-part series on the FDA defense. Copyright 2001 by the authors. Replies to this commentary are welcome]

A. Who Is Dr. John Gueriguian?

Dr. Gueriguian was the first medical officer assigned to the Rezulin (troglitazone) review process. At the time, Dr. Gueriguian was a 16-year veteran with the Food and Drug Administration assigned to the Metabolic and Endocrine Division. He helped create the clinical trial protocols and reviewed the IND and NDA submission.

Discovery has revealed early memos where Dr. Gueriguian repeatedly expresses concern about the safety of the drug in light of the body's tendency to store or sequester the drug in tissue as well as the drug's impact on fluid retention. Warner-Lambert/Parke-Davis internal memoranda confirm that Dr. Gueriguian repeatedly questioned the company about safety as well as efficacy issues. Dr. Gueriguian had the following valid concerns:

1. Rezulin was not safe because it was sequestered in the body tissues.

2. Rezulin caused fluid retention leading to liver and heart enlargement.

3. Rezulin was toxic to the liver.

4. Rezulin's efficacy was not impressive. Warner Lambert/Parke Davis inappropriately designed the protocols of the clinical studies to skew the data on the efficacy of Rezulin. Dr. Gueriguian had concerns that the

drug manufacturer was narrowing and changing the patient population selection to improve study results.

(See Exhibit A at end of commentary.)

Deposition of Robert Zerbe (12-14-00)
Sr. VP World Wide Clinical Research
Questions by Rainey Booth

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Q. Was your understanding that Dr. Gueriguian was challenging the company on issues of safety and efficacy, at least in part?
A. Yeah. My impression was he was challenging on a whole number of fronts: Safety, efficacy, trial design, a number of — you know, everything that he could find to be critical, he was.

B. Dr. Gueriguian's Medical Officer's Review Of Troglitazone

Dr. John Gueriguian prepared a draft review of the drug, troglitazone. Traditionally, medical officer reviews are presented to the advisory committee and form the basis of the FDA's presentation at the committee meeting. Before Dr. Gueriguian's review could become final, he was removed from the review process and his opinions were never presented to the advisory committee. Instead Dr. Fleming, his superior, made the presentation on behalf of the FDA and Dr. Fleming did not either mention Dr. Gueriguian's concerns or provide the committee with a copy of the draft review.

(See Exhibit B.)

C. Warner Lambert / Parke Davis' Response

Warner Lambert/Parke Davis' response to the removal of Dr. Gueriguian is not consistent and in direct contradiction to the documents and testimony. The company first claims that they did not consider Dr. Gueriguian to be a problem until he acted unprofessionally during two meetings with Mary Taylor on September 4 and September 26, 1996. Because of Dr. Gueriguian's threats and vulgar language during those meetings, Warner Lambert/Parke Davis felt obligated to file an official complaint. However, other than reporting his behavior, the company maintains that it did not ask for Dr. Gueriguian's removal, request his removal or influence his removal. Indeed, the company maintains that he posed no threat to the approval of troglitazone.

Deposition of Mary Taylor (10-31-00)
Regulatory Affairs Liaison
Questions by Rainey Booth

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Q. Okay. If you could take me through that meeting. Who said what? What was discussed?

A. At this point, Dr. Gueriguian was quite distressed over the fact that the agency, his group leader and had overruled him . . . on the priority review.

Q. Did he seem angry during this September 25th meeting?

A. I would say yes, he was angry, that is he was — in lots of different ways. . . . This is a man that is basically yelling across, you know, a very small little tiny office, at me saying, you know, at the top of his lungs. There is a lot of swearing in between, and repeatedly, and he was more than angry. In some respects he appeared to be out of control.

Q. In your affidavit you indicated that . . . "he called the company dishonest, and crooks." Did he specifically reference individuals, or a factual basis for that, or did he just use those terms?

A. He used those terms.

Q. The next sentence, he said, "the CEOs have dollar signs in their eyes." Did he give you any factual basis for that?

A. No, he did not.

Q. Just made the statement?

A. Yes.

Q. Do you interpret it as a threat being made by Dr. Gueriguian at your company?

A. Absolutely. I mean, what he was saying, if you don't withdraw this, you know, I'm going to cause you a problem.

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Q. Are you aware of whether there was ever a decision or conclusion reached at the company, Parke-Davis, that as long as Dr. Gueriguian was the Medical Reviewer, that the approval process with Rezulin was going to face impediments or problems that it would not otherwise have?

A. No.

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Q. To the best of your knowledge, did the company ever request or recommend that Dr. Gueriguian be removed as Medical Reviewer?

A. No.

Deposition of Irwin Martin (1-15-01)
Vice President International Regulatory Affairs

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Q. Prior to the meeting with Mary Taylor and John Gueriguian that you just described that you heard about, was it your perception that the chances of troglitazone being approved were greater if John Gueriguian was not the medical officer or was the medical officer?

A. We did not need John Gueriguian off the drug. I mean, I need to make that very clear. John could have continued through the review, could have finished his medical officer review, could have written the whole thing up, still could have recommended nonapproval, could have spoken at the advisory committee, and we still would have been approved. . . .

Q. So your perception — prior to the Mary Taylor meeting that we've discussed in September — your perception was that John Gueriguian would have had no effect on whether the drug was approved?
A. . . . Would we not have been approved if John stayed? We would have been approved. I am convinced of that.

Deposition of Robert Zerbe (12-14-00)
Sr. VP World Wide Clinical Research

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Q. Was it your impression, with Dr. Gueriguian's removal, there was a better chance of Rezulin being approved?
A. It was my impression that was the case. . . .

However, documents show that, as early as 1995, there was consideration being made at the FDA concerning Dr. Gueriguian. In an Aug. 7, 1995, Parke-Davis record of FDA contact, Dr. Fleming is reported to have offered to "ease him out." An Oct. 16, 1996 internal memo celebrating the company's having got over the "JG Hurdle," is a final nail in the coffin. In the 1996 memo, the company admits "they did what others would have liked to" and that they are over "the JG hurdle" and that John "is no longer an unknown timebomb."

(See Exhibit C.)

Clearly Warner Lambert/Parke Davis used their tremendous political pressure to get Dr. John Gueriguian removed from the troglitazone approval process because he had strong and definitive opposition to the drug. Without him as the medical officer, the drug was easily approved. The question remains unanswered whether he is a hero or a buffoon?

Deposition of Irwin Martin (1-15-01)
Vice President International Regulatory Affairs

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Q. Now, you said earlier that John Gueriguian is no hero. Tell me what you mean by that.
A. John Gueriguian had no insight to this NDA. He had the worst insight to this NDA. If he actually found hepatotoxicity, which he did not, he did nothing about it. . . . So the fact that John thinks that he was overruled because he saw something about hepatotoxicity — it's absurd. John's a buffoon — excuse the expression — and the fact that people think he's now a hero is insulting. It's insulting to us. ■

Parke-Davis

RECORD OF FDA CONTACT

Date: 1/10/94	Dr. Gueriguian restated his opinion that approval of this drug would be based on the risks versus the benefit. It didn't matter to him if we looked at the completion rate as a primary endpoint; the benefit would need to outweigh the risk in the long run. Troglitazone has a long half-life, large volume of distribution and is very hydrophobic. Pharmacokinetic principles, therefore, indicate that the drug is being sequestered somewhere in the body. We must make an effort to determine where the drug is being stored and what the potential toxicities are This would be considered a strong predictor for potential toxicity and must be addressed decisively. We must remember that troglitazone will be used very long term, if approved, and we must make sure chronic use is safe. Dr. Gueriguian indicated that he was willing to meet with us to discuss compartmentalization of troglitazone and the best ways to assess long-term safety as he has a lot of experience in this area.
Date: February 17, 1994	Dr. Guerigian responded that : main goal in raising this issue was to make the company sensitive to the fact that there were potential safety issues associated with a large volume of distribution and that adequate safety monitoring during clinical trials was necessary.
Date: February 25, 1994	We must make sure that we evaluate all available preclinical studies for adverse effects especially those common across species and take this information into consideration as we monitor our clinical trials. If we are interested, he is still willing to sit down and discuss sequestering and/or monitoring with us.
Date: Thu, Aug 03, 1995	Dr. Gueriguian felt that we were not listening to his ideas and were simply trying to convince him to support our design.
Date: Fri, Aug 23, 1996	I explained to Dr. Fleming why the indication section was changed; we actually tightened the intended population to eliminate patients who had failed SU to go directly to troglitazone without going onto insulin. We had done this since we did not have data to support this switch in the initial NDA. Dr. Fleming did not appreciate this change and stated that this explanation explained Dr. Gueriguian's statement during the filing meeting. He had said that we had changed "the population" and these patients were not SU failures.
Date: Wed, Sep 04, 1996	Dr. Gueriguian felt that our study results were confusing and showed me his summary of our data. Dr. Gueriguian stated that he did not agree to the protocol and if we had followed his suggestions "Parke-Davis would not be in this mess".

EXHIBIT A

NDA 20720
Sponsor:Parke-Davis
Drug:Troglitazone

Received:9/6/96
Reviewed: /93
Doct: N20720A/G121

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION

11.7 Adverse reactions

Should be rewritten to indicate, in simple words and sentences, the various area were significant adverse events may be encountered (cardiovascular, neuropsychiatric, and hepatic).

12 CONCLUSIONS

This drug has not been shown to represent a significant therapeutic advance, as alleged by the company.

13 REVIEWER'S RECOMMENDATIONS

This Reviewer recommends non-approval of this NDA

Parke-Davis

Record of FDA Contact

Date: Tue, Nov 26, 1996

Summary:

Dr. Fleming provided a copy of Dr. Gueriguian's Medical Officer Review (MOR) of troglitazone (circulated separately). He requested that we provide him comments in rebuttal of Dr. Gueriguian's review. He will annotate the review with both his and our comments. As Dr. Fleming has no other MOR to use, Dr. Gueriguian's must serve as the official review, even though it is incomplete. Dr. Fleming plans to complete it and use it as the backgrounder for the Advisory Committee. If not provided with a MOR, the committee would be concerned and feel the presentation incomplete. Thus, Dr. Fleming feels he has no option but to use and comment upon Dr. Gueriguian's review.

Dr. Fleming agreed that we could recommend certain sections be deleted as they may be inflammatory. He also agreed to provide us with a final copy of what goes to the committee before it goes to the committee.

Fleming stated to both Dr. Cresswell and me that Dr. Gueriguian was clearly biased in his review and his comments in the review "went over the line." He will "strongly" annotate the review disagreement with Dr. Gueriguian's assessment.

EXHIBIT B

Parke-Davis

Record of FDA Contact

Date: Mon, Aug 07, 1995

Dr. Fleming asked me to call Dr. Gueriguian for the results of their discussion. He would prefer that I call to keep him (Dr. Fleming) out of the loop. Although he did ask me to call him back and let him know the results of our discussion. He also offered that if our discussion did not go well, he would ease Dr. Gueriguian out.

Date: 10/16/96 9:11:11 PM
From: Irwin Martin
Subject: Fleming call; Weds. pm
To: WILLIAM MERINO
CC: MARY TAYLOR
CC: IRWIN MARTIN

FAXED To you at PhRMA

Bill-
Zan called back near 6pm on Weds. We spoke about a number of things. I wrote up a contact sheet on the advisory committee issues. Will not on the following.

Zan clearly knew all about the issues with the internal affairs folks and Mary's meeting, etc.
John is "out of the picture." His review is complete, though not finalized. It will not get to the adivsory committee, but may very well wind up in the public record after approval as it is part of the review. Zan is now the primary reviewer and is using Misbin as a consultant. Misbin offers a "balance" as he is skeptical, but he may have been influenced too much by John. Only Zan will present medical to the advisory committee.

Zan has "absolutely no concerns at all" with Mary or I handling continued liaison functions. He understands this was all done very professionally.

He remains worried that John would try to find a sympathic yellow journalist and try to go public. I mentioned the story about he and John and the last NDA approval which was in the "white" sheet. He hadn't seen it and asked for a copy. He was concerned that their disagreement was now public. I replied that it seemed like John's response wasn't merely a PD issue and that we did what many others would have liked to. Zan agreed and thought we should get some award from PhRMA for our actions. (He took this all in friendly manner.)

The conversation was constructive and centered primarily on the adivsory committee. As far as the NDA goes, it seems we're over the JG hurdle. We still have much to deal with, but at least John is no longer an unknown timebomb.

-Irwin

EXHIBIT C