

**REPORT ON TRASYLOL®**

**FOR**

**BAYER CORPORATION  
AND  
BAYER AG**

**BY**

**ZUCKERMAN SPAEDER LLP**

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## EXECUTIVE SUMMARY

On September 21, 2006, the drug aprotinin, marketed by the Bayer Pharmaceuticals Corporation (“BPC”) in the United States under the trade name Trasyolol®, was the subject of a meeting of the Food and Drug Administration’s Cardiovascular and Renal Drugs Advisory Committee. The following week, BPC learned that two leaders in the Global Drug Safety (“GDS”) unit of its affiliate company, Bayer Healthcare AG in Germany (“BHC-AG”), had received preliminary results from an observational safety study of Trasyolol prior to the Advisory Committee meeting. This study was conducted by the i3 Drug Safety research firm (“i3”) under the leadership of Dr. Alexander Walker (the study is referred to as the “i3 study”). At no time before or at the Advisory Committee meeting did BPC or BHC-AG (collectively, “Bayer”) inform FDA about the i3 study’s existence or its preliminary results and conclusions.

On September 27, 2006, Bayer notified FDA of those preliminary results.

In February 2007, Bayer retained Zuckerman Spaeder LLP<sup>1</sup> to conduct an investigation of the delay in disclosure. It asked the firm to address four main questions. The following are the four questions we were asked to answer and a summary of the answers. We explain our conclusions in more detail thereafter.

**Question #1: Who at Bayer knew of the existence of the i3 study and which of those persons, if any, were functionally responsible for informing FDA of its existence?**

**Answer to Question #1:** Many employees of both BPC and BHC-AG knew of the i3 study. Bayer employees and executives who were aware the study was being conducted in the period between June 19, when BHC-AG signed the contract with i3, and September 21, when the Advisory Committee meeting occurred, include (in alphabetical order): Conny Berlin, Department of Integrated Analysis; Pam Cyrus, Vice President for Trasyolol and Non-Specialty Products, US Medical Affairs; Howard Dorfman, Head of Patents, BPC Legal; Tomasz Dyszynski, International Drug Safety Manager for Aprotinin; Allen Heller, Vice President of Medical Science, U.S. Pharma Division; Hans-Peter Kraemer, Head Systems and Operations, GDS; Paul MacCarthy, Vice President, Head of Medical & Scientific Affairs (North America); Kemal Malik, Global Head of Development and Chief Medical Officer; Andrea Nadel, Deputy Director of Statistics, BPC; Michael Rozycki, Director of US Regulatory Affairs; Joseph Scheeren, Senior Vice President of Global Regulatory Affairs; Anita Shah, Global Project Leader, BPC; Kuno Sprenger, Risk Manager and Drug Safety Advisor for GDS; Ed Tucker, Vice President, U.S. Drug Safety Assurance; Terry Taylor, Vice President, Global Clinical Development; David van Veenhuizen, Global Clinical Leader, Trasyolol; and Ernst Weidmann, Vice President for GDS.

Bayer’s Global Regulatory Affairs department had functional responsibility for communicating with FDA about Trasyolol. Dr. Joseph Scheeren is the Senior Vice President of

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<sup>1</sup> On October 13, 2006, Bayer announced that it had retained Fred Fielding, then of the Washington, DC law firm Wiley Rein & Fielding, to investigate the Trasyolol matter. On January 8, 2007, Fielding was named White House Counsel by President Bush. On February 7, 2007, Bayer officially retained Zuckerman Spaeder LLP to conduct the independent Trasyolol investigation as Fielding’s replacement.

Global Regulatory Affairs. Dr. Michael Rozycki is the Director of US Regulatory Affairs. Dr. Rozycki served as Bayer's primary liaison to FDA on Trasylol-related matters throughout 2006, including all matters related to the Advisory Committee meeting.

**Question #2: Why was the existence of the i3 study not communicated to FDA in advance of the Advisory Committee meeting on September 21, 2006?**

**Answer to Question #2:** The highest levels of Bayer management responsible for preparing for the Advisory Committee meeting agreed that Bayer should and would disclose the ongoing study before the meeting. The managers responsible for making that disclosure ultimately failed to do so. We conclude that the failure to disclose was not motivated by an intent to conceal the i3 study from FDA or the Advisory Committee but was regrettable human error. Several factors contributed to this error.

First, BPC's regulatory affairs leaders responsible for the FDA relationship believed erroneously that the i3 study's preliminary results would not be available until months after the Advisory Committee meeting.

Second, BPC's scientific leaders opposed contracting for the i3 study because they were skeptical about its potential scientific value. This negative view colored the approach to disclosure.

Third, the study did not undergo BPC's formal review procedures.

Fourth, Bayer management handled the study in a way that diminished its visibility and importance to the BPC leaders. Management assigned responsibility for the i3 study to Dr. Weidmann and Dr. Sprenger in Germany without establishing clear lines of communication to the BPC leaders coordinating Bayer's preparation for the Advisory Committee meeting; thus, the i3 study was a secondary priority in the minds of these BPC leaders.

As a result of these factors, BPC focused its attention on other projects it considered more directly important to the Advisory Committee meeting.

**Question #3: Which employees of Bayer received, or otherwise knew about, the findings and conclusions of the i3 study in advance of the Advisory Committee meeting on September 21, 2006?**

**Answer to Question #3:** Only two people at Bayer received or otherwise knew about the findings and conclusions of the i3 study in advance of the Advisory Committee meeting: Dr. Ernst Weidmann, the Vice President for GDS; and his associate Dr. Kuno Sprenger, Bayer's Risk Manager and Drug Safety Advisory for GDS. They received the Preliminary Report for the i3 study no later than September 14, 2006.

**Question #4: Why were the findings and conclusions from the Preliminary Report of the i3 study not communicated to FDA in advance of the Advisory Committee meeting?**

**Answer to Question #4:** Bayer did not disclose the findings and conclusions from the Preliminary Report on or before September 21, 2006, because Drs. Weidmann and Sprenger did not advise BPC, FDA, or the Advisory Committee that they had received the Preliminary Report. Drs. Weidmann and Sprenger concluded that the i3 study as executed departed substantially from the March 2006 proposal upon which it was based. Drs. Weidmann and Sprenger identified serious questions about the study's quality. They articulated these concerns in written questions provided to i3 on September 18. When Drs. Weidmann and Sprenger did not receive responses to their questions before the Advisory Committee meeting, they considered disclosure scientifically premature.

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Section I of the Discussion provides basic background information about the regulatory history of Trasylol, the scientific publications that prompted FDA to schedule an Advisory Committee meeting, and relevant events in the months before that meeting. Section II summarizes the results of the investigation as to Question Nos. 1 and 2. Section III summarizes the results of the investigation as to Question Nos. 3 and 4.

## DISCUSSION

### I. Introduction and Background

#### A. History of Trasylol

Use of aprotinin, a drug derived from bovine lung, dates to the 1950s and was originally administered to treat pancreatitis. On December 28, 1993, the U.S. Food and Drug Administration ("FDA") approved Bayer's new drug application (NDA 020304) to permit physicians to administer Trasylol for "prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of repeat coronary artery bypass graft surgery" and "in selected cases of primary coronary artery bypass graft surgery where the risk of bleeding is especially high. . . ." On August 28, 1998, FDA approved Bayer's application to expand Trasylol's label to permit its use in all coronary artery bypass graft ("CABG") surgery.<sup>2</sup>

#### B. The Mangano and Karkouti Studies

On January 26, 2006, the *New England Journal of Medicine* published an article entitled "The Risk Associated with Aprotinin in Cardiac Surgery." The article, which described a prospectively designed observational study by Mangano, *et al.*, concluded that Trasylol use in CABG surgery was associated with a higher risk of dialysis or creatinine increase, myocardial infarction or heart failure, stroke, encephalopathy, or coma. The report suggested that aprotinin had a greater association with adverse events compared to tranexamic acid and aminocaproic acid, the two other agents used to limit bleeding during or after CABG surgery.

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<sup>2</sup> Bayer's 2006 data analysis revealed a previously undetected association between Trasylol use and elevated serum creatinine levels. This led to labeling changes in 2006 to reflect the new information.

On January 20, 2006, the on-line edition of the journal *Transfusion* had published “A Propensity Score Case-Control Comparison of Aprotinin and Tranexamic Acid in High-Transfusion-Risk Cardiac Surgery.” This report of a prospective observational study by Karkouti, *et al.*, indicated that patients receiving Trasylol experienced a higher rate of renal dysfunction compared to patients receiving tranexamic acid.<sup>3</sup>

### **C. FDA’s Response to the Mangano and Karkouti Studies**

In response to these articles, on February 8, 2006, FDA issued a Public Health Advisory and Questions and Answers information sheet on Trasylol, and indicated its intention to seek input from an advisory committee. In late May 2006, FDA set a meeting of the Cardiovascular and Renal Drugs Advisory Committee for September.<sup>4</sup> FDA’s decision to schedule an advisory committee meeting dedicated solely to Trasylol reflected the agency’s concern about the drug’s safety profile.<sup>5</sup>

### **D. BPC’s Response to the Mangano and Karkouti Studies**

Bayer received a pre-publication copy of the Mangano article and immediately mobilized to respond. It created a Trasylol Steering Committee (“TSC”) to oversee all Bayer activities involving aprotinin. Dr. Kemal Malik, Global Head of Development and Chief Medical Officer, led the TSC. Dr. MacCarthy, Dr. Scheeren, Dr. Rozycki, Stephen Zaruby (Vice President, Global Head for Trasylol Business Unit), Howard Dorfman, and Dr. Anita Shah were the BPC members on the TSC. Dr. Weidmann, Dr. Max Wegner (Head Therapeutic Area Cardiovascular and Risk Management at Global Regulatory Affairs), Ulrike von Schmeling (a German AG attorney), and Franz-Joseph Wingen (Head Medical Science, Europe) were the BHC-AG members on the TSC. Bayer also created a separate Advisory Committee Steering Committee, led by Dr. MacCarthy, to coordinate Bayer’s preparation for the Advisory Committee meeting.

From the outset, through Dr. Malik, Bayer committed to an internal policy of “total transparency” with FDA.

Bayer’s initial analysis revealed inconsistency between Mangano’s and Karkouti’s reported results and Bayer’s body of clinical data for Trasylol. However, Bayer lacked its own data comparing the safety of Trasylol to the safety of aminocaproic acid or tranexamic acid, in part because neither of those two drugs had been FDA approved for use in CABG surgery. Bayer, accordingly, set out to collect and examine all data it could locate on aprotinin – both from Bayer-sponsored studies as well as from the body of scientific literature worldwide. Bayer launched this project, described by many as a monumental undertaking, under the direction of Dr. Pam Cyrus, Vice President for Trasylol and Non-Specialty Products.

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<sup>3</sup> The descriptions of the studies’ findings are drawn in part from FDA’s 2006 public pronouncements.

<sup>4</sup> FDA provided formal notice of the meeting date to Bayer by letter dated June 23, 2006.

<sup>5</sup> In general, FDA utilizes advisory committees “to conduct public hearings on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner.” 21 C.F.R. § 14.5. The function of the Cardiovascular and Renal Drugs Advisory Committee is to review and evaluate data “on the safety and effectiveness of marketed and investigational human drugs for use in cardiovascular and renal disorders.” 21 C.F.R. § 14.100(a)(5)(ii).

BPC also initiated a second project, which involved an intensive review and analysis of the Mangano and Karkouti studies. Dr. Allen Heller, Vice President of Medical Science in the U.S. Pharma Division, in close consultation with outside experts, led this second project. Dr. Heller's team found serious methodological and statistical flaws in the Mangano study and sent FDA a written critique.

#### **E. BHC-AG's Response to the Mangano and Karkouti Studies – the i3 Study**

Global Drug Safety in Germany initiated a third Bayer response to the Mangano article. Dr. Weidmann, Vice President for GDS, felt Bayer should generate its own independent data comparing Trasylo1 to other antifibrinolytic agents. Drs. Weidmann and Sprenger concluded that a randomized controlled clinical trial comparing the various antifibrinolytic agents would not be practical, and viewed a well-designed observational study as the best alternative. Dr. Weidmann considered this study an "addendum" to Bayer's two other major undertakings in response to the Mangano paper.

To that end, on February 1, 2006, Dr. Sprenger contacted Dr. Alex Walker, a highly respected Harvard-trained physician and pharmaco-epidemiologist and the Senior Vice President for Epidemiology at i3.<sup>6</sup> Dr. Sprenger asked Dr. Walker to consider designing an observational study that would permit analysis of Mangano's conclusions.<sup>7</sup> i3 provided initial "concept letters" to Dr. Sprenger on February 9 and February 16. On March 3, 2006, John Seeger, Dr. Walker's associate at i3, emailed Dr. Sprenger and Dr. Weidmann a more formal proposal titled "Aprotinin and Cardiovascular and Renal Outcomes: Study Proposal" ("March 3 Proposal"). i3 proposed to base its study on the Premier Perspective Comparative Database.<sup>8</sup> It called for delivery of preliminary results based solely on information in the Premier database within six months of the execution of contract.

TSC members debated i3's March 3 Proposal. Dr. MacCarthy in particular felt the i3 study should not be undertaken because he and others questioned the Premier database's ability to permit a scientifically meaningful assessment of the various antifibrinolytics agents' relative risks. Dr. Malik proposed that Bayer obtain an independent evaluation of the March 3 Proposal from a consulting expert. Dr. Weidmann engaged a McGill University epidemiologist, Samy Suissa, for that purpose. Dr. Suissa returned a favorable evaluation. After clearance from the BPC legal department, Dr. Malik approved the i3 study on June 1, and the TSC concurred at its June 13 meeting. On June 19, 2006, an i3 representative and Dr. Weidmann signed a contract and the study began. At Dr. Sprenger's urging, the appendix to the contract shortened the period for delivering preliminary results to three months, in time for the September 21, 2006 Advisory Committee Meeting. Although Dr. Sprenger says he told BPC about the compressed timeline,

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<sup>6</sup> i3 Drug Safety is part of Ingenix, a subsidiary of UnitedHealth Group. Several people, both at Bayer and i3 Drug Safety, noted that FDA considers i3 Drug Safety a reliable and trusted source of independent scientific judgment and information. Indeed, i3 Drug Safety's reputation was the reason Dr. Sprenger approached Dr. Walker about conducting the Trasylo1 safety study.

<sup>7</sup> The attached timeline recounts in more detail the evolution, review, and approval of the i3 study within Bayer from March to June 2006.

<sup>8</sup> The March 3 Proposal described the Premier database as "the largest hospital-based, service-level comparative database in the country providing detailed resource utilization data along with patients' primary and secondary diagnosis and procedure codes."

leaders at BPC denied ever learning of the revised timetable. The actual contract containing the compressed schedule was never circulated within BPC.

#### **F. Events Relating to the i3 Study from June 2006 to September 2006**

Between the TSC's approval of the i3 study in June 2006 and the September 21, 2006, Advisory Committee meeting, BPC continued its extensive substantive and logistical preparation for the Advisory Committee meeting. The choreographed presentation required preparation of thousands of slides that would allow Bayer to respond to the Advisory Committee's questions. It also required a team of people to develop comprehensive knowledge of the slides and their contents, as well as a system to recall any slide at a moment's notice. Dr. Rozycki acted as the "executive producer" of Bayer's overall effort. He coordinated the work of dozens of participants at each of three weekend "mock panel" preparation sessions in New York City (July 22, August 19, and September 9), a dress rehearsal the day before the Advisory Committee meeting, and the Advisory Committee meeting itself. Dr. Rozycki also acted as Bayer's moderator at the Advisory Committee meeting and made the company's introductory presentation.

During this period, BPC had numerous communications with FDA on both substantive and logistical matters, with Dr. Rozycki serving as BPC's lead contact. On June 28, 2006, Bayer and FDA held a conference call regarding the Advisory Committee meeting. Dr. Scheeren recalled a Bayer agenda item to inform FDA about the i3 study on that call. According to Dr. Scheeren, the conference call ended for lack of time before Bayer could discuss the study. Other BPC personnel we interviewed, including Dr. MacCarthy and Dr. Rozycki, do not recall an intention to disclose the i3 study during this call. Dr. Rozycki's FDA contact report summarizing the June 28 call reflects an FDA questioner asking "whether Bayer had any other questions to discuss." According to Dr. Rozycki's report, Bayer's response was to ask whether Mangano and Karkouti's would attend the Advisory Committee meeting.

On July 17, Bayer and FDA had a meeting to review BPC's data submissions relating to the Advisory Committee meeting. The day before, several Bayer scientists, regulatory leaders, and external consultants met at a hotel near FDA headquarters in Maryland to prepare. Several people told us they learned about the i3 study from Dr. Sprenger for the first time that day. The group agreed Bayer should inform FDA of the i3 study during the July 17 meeting. Drs. MacCarthy, Scheeren, and Rozycki were responsible for doing so. If FDA were to request further information, Dr. Sprenger would be ready to provide it. Dr. Sprenger told us he informed at least Drs. Scheeren and MacCarthy that the i3 study would yield results before the Advisory Committee meeting. Everyone else we spoke to who attended the July 16 meeting denied this. Nevertheless, Bayer attendees at the July 17 meeting with FDA told us discussion of the i3 study never occurred because of an unexpected debate about whether improvements in blood supply safety rendered Trasylol unnecessary.

On August 17, BPC submitted a massive briefing document to FDA for the Advisory Committee meeting. In mid-July, Dr. Seeger had suggested to Drs. Weidmann and Sprenger that the August 17 briefing document should at least mention the i3 study because the actual study results would not be available for inclusion by the August 18 deadline. We found no indication

that Dr. Weidmann or Dr. Sprenger shared Dr. Seeger's recommendation with anyone at BPC. No mention of the i3 study made its way into the August 17 briefing document.

The i3 study was also briefly discussed at least at one of the mock panels Bayer conducted. For example, several participants recalled brief discussion of the i3 study at the August 19 session. In particular, these participants recalled Dr. Sprenger reporting that results of the i3 study would *not* be available before the Advisory Committee meeting. Dr. Sprenger denies this version of events, asserting he told BPC colleagues on more than one occasion that the i3 study results would be available before the Advisory Committee meeting. Notwithstanding these discussions of the i3 study, however, they did not cause Dr. Rozycki or anyone else to take affirmative steps to tell FDA about it.

Dr. Weidmann told us that, several times between July 2006 and the Advisory Committee meeting, he asked Dr. Scheeren why Dr. Scheeren had not yet told FDA about the ongoing i3 study. According to Dr. Weidmann, Dr. Scheeren responded that regulations did not require disclosure.<sup>9</sup> Dr. Weidmann also said he told Dr. Scheeren that the timelines for the i3 study had been shortened to produce preliminary results before the Advisory Committee meeting. Dr. Scheeren denies that any of the conversations occurred, and denies having heard about the modified study timeframe from Dr. Weidmann or anyone else. These conflicting accounts cannot be resolved. What is undisputed is that both of these individuals acknowledge having had a close personal and professional relationship such that one-on-one conversations between them likely took place.

On September 7, 2006, Dr. Weidmann and Dr. Sprenger each recirculated the March 3 Proposal to Drs. MacCarthy, Scheeren, and Tucker.<sup>10</sup> In response, minutes after having received the i3 study proposal from Dr. Weidmann, Dr. Scheeren forwarded Dr. Weidmann's email to Dr. Rozycki with the note, "Mike – We need to discuss this as well." Dr. Scheeren recalled speaking with Dr. Rozycki after this email. Although Dr. Scheeren denied a detailed recollection of the conversation, he said that an "unconscious decision" "could have" been made to delay disclosure until after the Advisory Committee meeting. He thought Dr. Rozycki "could have" left that meeting with a sense that the timing of the disclosure was "in the air" (i.e., undecided), and "maybe" Dr. Rozycki thought disclosure could occur after the September 21 Advisory Committee meeting.

Dr. Rozycki has no recollection of any discussion with Dr. Scheeren (or anybody else) in response to this email. He does recall that the email jogged his memory of not having told FDA about the study. Dr. Rozycki did not recall any discussion, whether or not about the email,

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<sup>9</sup> The view that FDA regulations did not require the existence of the ongoing i3 study to be immediately disclosed to FDA or the Advisory Committee was shared by others at BPC, including Drs. MacCarthy and Rozycki. This view appears supported by relevant FDA regulations governing the reporting requirements for the sponsor of a drug after its approval for marketing. *See* 21 C.F.R. § 314.80-314.81. There was consensus among Bayer people we spoke with that BPC was required to disclose results of such a study if the results had any potential impact on the drug's labeling and/or risk-benefit profile.

<sup>10</sup> This recirculation coincided with Drs. Weidmann and Sprenger learning that i3 was ready to discuss preliminary results from its study. The close timing of these events raised the possibility that GDS intended the recirculation as notice to their American colleagues that results were imminent. However, Dr. Weidmann denied having sent this email with this purpose. Dr. Sprenger indicated he sent the email to remind BPC about the i3 study. Nothing about the email would have led its recipients to understand that results would soon be forthcoming.

that caused him to believe he had been relieved of responsibility to inform FDA about the i3 study. However, nothing about the email caused Dr. Rozycki to believe he must inform FDA about the i3 study in the two weeks before the Advisory Committee meeting.

On September 20, Bayer held its dress rehearsal for the Advisory Committee meeting at a hotel in Bethesda Maryland. Several witnesses recall Dr. Scheeren asking Dr. Weidmann about the status of the i3 study. Dr. Weidmann was heard to respond that no results were yet available. Both Drs. Weidmann and Sprenger deny the study was a topic of discussion at that rehearsal.

On September 21, the Advisory Committee conducted an all-day meeting on Trasylol. No one from Bayer mentioned the i3 study.

## **II. The i3 Study – Who at Bayer Knew About It, and Why Was Its Existence Not Disclosed to FDA in Advance of the Advisory Committee Meeting?**

This section of the Report identifies the executives and employees at Bayer who knew about the i3 study before the Advisory Committee meeting, and focuses on why these people failed to disclose the i3 study to FDA in advance of that meeting. This latter question proved the most difficult issue in the investigation. In summary, we conclude that many people knew about the i3 study, and that there was no conscious decision or effort to conceal information about the i3 study from FDA or the Advisory Committee.

### **A. Who knew about the i3 study?**

Many employees both at BPC and BHC-AG knew of the i3 study, first as a proposal in early March 2006 and then after June 19, 2006, when Bayer committed to proceed with the i3 study. Bayer personnel aware of the study's existence in the period after June 19 include (in alphabetical order): Conny Berlin, Pam Cyrus, Howard Dorfman, Tomasz Dyszynski, Allen Heller, Hans-Peter Kraemer, Paul MacCarthy, Kemal Malik, Andrea Nadel, Mike Rozycki, Joseph Scheeren, Anita Shah, Kuno Sprenger, Ed Tucker, Terry Taylor, David van Veenhuyzen, and Ernst Weidmann.<sup>11</sup>

### **B. Why was FDA not informed of the i3 study's existence?**

Most of the core participants blame collective human failure for Bayer's failure to tell FDA about the i3 study before the Advisory Committee meeting. The investigation found no evidence to suggest anyone at Bayer deliberately hid the existence of the i3 study from FDA. The accounts and explanations of centrally involved participants are substantially consistent on this point. BPC managers and employees did, however, offer divergent accounts of *when* they believed BPC intended to inform FDA of the i3 study. Dr. MacCarthy and Dr. Malik, for example, assumed disclosure would occur at the earliest opportunity. Dr. Rozycki, on the other hand, believed he would tell FDA about the i3 study when more concrete information came to light. As noted above, ample opportunities to discuss the i3 study with FDA came and went without disclosure.

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<sup>11</sup> Others at Bayer, such as Stephen Zaruby, Franz-Joseph Wingen, and Ulrike von Schmeling received emails with the i3 study proposal attached, but the investigation showed they had limited familiarity or involvement with the study.

## 1. Operational factors

Dr. Rozycki acknowledges his primary responsibility for disclosing the i3 study to FDA. Several reasons explain Dr. Rozycki's failure in this regard. First, Dr. Rozycki told us that neither he nor his BPC colleagues expected results from the i3 study until well after the September 21 Advisory Committee meeting. Dr. Rozycki felt others must have shared this assessment because no one ever directed him to take the steps necessary to disclose the i3 study by a particular date such as before the Advisory Committee Meeting. Second, Dr. Rozycki had internalized the negative view of the i3 study held by his BPC colleagues, and he received no information – from Germany or elsewhere – that illuminated, allayed, or addressed these concerns. Thus, telling FDA about the i3 study's existence was of little relevance to Dr. Rozycki compared to preparing BPC's presentation of the voluminous scientific information that was centrally important to FDA and the Advisory Committee. The i3 study also fell outside Bayer's clinical study review process, and thus outside the regulatory reporting procedures that apply to such studies.

*a. BPC believed the i3 study would not yield results until months after the Advisory Committee meeting.*

Documents we reviewed and the substantially consistent recollections of those involved support Dr. Rozycki's claim that he operated with the understanding that preliminary results would not be ready until months after the Advisory Committee meeting. Several times, as late as September 7, members of the TSC received copies of the March 3 Proposal. For those recipients who read it, the March 3 Proposal's timeline reinforced that preliminary study results would be delivered six months from when the study began, which they knew to be June. Although the actual contract between BHC-AG and i3 shortened the deadline to three months, no one in the US saw the contract. (Again, however, Dr. Sprenger told us he repeatedly announced that preliminary results were expected before the Advisory Committee.)

Furthermore, according to several witnesses, at one of the mock panels, Dr. Sprenger confirmed that results would not be available before the Advisory Committee meeting. Dr. Sprenger asserted, to the contrary, that he had told his BPC colleagues, both at the July 16 meeting as well as at the August 19 mock panel, that results would arrive before the Advisory Committee meeting. While we do not resolve the conflict in these accounts, Dr. Rozycki insisted that BPC, and he personally, would have made informing FDA a top priority had he suspected any chance of results from the i3 study before the Advisory Committee meeting. Other witnesses told us they were flabbergasted upon learning results had been delivered before the September 21 meeting.<sup>12</sup>

*b. BPC opposed the i3 study.*

Leading scientists at BPC – including Drs. MacCarthy, Heller, and Cyrus, who were all intimately involved in the Advisory Committee preparation – perceived inherent methodological limitations in the i3 study. They believed any retrospective study would suffer from similar, if

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<sup>12</sup> A list of potential Advisory Committee questions prepared by BPC contained a query regarding the results of “an observational study” Bayer is conducting. On his version dated September 19, Dr. Weidmann wrote “no results yet.” Weidmann claimed his notation did not refer to the i3 study.

not identical, flaws as those identified in the Mangano study. BPC scientists – when they learned about the i3 study – suspected that its GDS supporters had not adequately investigated the Premier database. These BPC individuals doubted the database’s power to complete the i3 study as proposed.

Dr. Rozycki did not at the time overtly link BPC’s negative feelings about the study to his failure to tell FDA about it. However this opposition to the study made him less inclined to take affirmative steps to raise the i3 study’s profile. Dr. Rozycki told us his Bayer US colleagues tacitly accepted this passive approach.

*c. BPC was preoccupied with preparation for the Advisory Committee meeting.*

BPC perceived the i3 study to be of comparatively little relevance to Bayer’s intense preparation for the Advisory Committee meeting. It therefore assumed a subordinate status. Indeed, Bayer allocated *no* time in its Advisory Committee presentation for discussion of the i3 study. Although Dr. Rozycki emphasized he would do things differently in hindsight, he also suggested that his failure to disclose the i3 study resulted from a defensible ordering of priorities under the circumstances. Lacking sufficient information about the i3 study to impart to FDA, and busy with more pressing priorities, Dr. Rozycki did not actively pursue the necessary information or seek the necessary approval to have a conversation about the i3 study with FDA. Further, no one ever instructed Dr. Rozycki to inform FDA by a date certain (such as before the Advisory Committee).

Dr. Rozycki’s intense schedule and the immense pressure under which he operated during these several months leading up to the Advisory Committee meeting frustrated his ability to exercise optimal project management. BPC employees, particularly Dr. Rozycki, were inundated with work.<sup>13</sup> Dr. Rozycki, the person responsible for actually making the regulatory contact with FDA, also had primary responsibility for overall coordination of Bayer’s preparation. Dr. Rozycki freely acknowledges having neglected certain outstanding “action items” – including disclosure of the i3 study to FDA.

*d. The i3 study did not undergo Bayer’s normal review processes.*

As a retrospective observational study, the i3 study fell outside the normal review and approval procedures applicable to clinical studies. Normally, when sponsoring a prospective clinical study, Bayer conducts an extensive internal review and approval process that culminates in submission of a study protocol to FDA. The i3 study was a retrospective database analysis and thus did not involve giving drugs to patients. As such, i3 never prepared a protocol beyond the initial March 3 Proposal (nor was development of a full blown protocol contemplated either by i3 or Drs. Weidmann and Sprenger). Dr. Rozycki cited the absence of a full protocol, as opposed to the March 3 Proposal, as an additional factor justifying his lack of focus on the i3

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<sup>13</sup> One person on the TSC had estimated that Bayer personnel put over 150,000 person-hours into the Advisory Committee meeting preparation. Several witnesses referred to 7-day, 80-plus hour workweeks in the months leading up to the Advisory Committee meeting.

study. Dr. Rozycki could not explain why he did not ask anyone at BPC or GDS for a protocol, or why he did not alert FDA about the study notwithstanding his limited information, except to reiterate that he did not perceive it as an important component of Bayer's Advisory Committee effort.

## 2. Structural factors

Bayer management permitted the i3 study to be handled in ways that frustrated Bayer's policy of openness. From the beginning, the Global Drug Safety unit at BHC-AG oversaw Bayer's involvement in the solicitation, development, and oversight of the i3 study. Dr. Weidmann signed the contract with i3 on behalf of Bayer and no one at BPC reviewed the contract. Further, the documents and interviews all confirm that GDS, specifically Drs. Weidmann and Sprenger, handled all communications between Bayer and i3. No one from BPC (including Ed Tucker, the U.S. Head of Drug Safety) had any contact with i3 about this study during the relevant period. Drs. Walker and Seeger of i3 confirmed never having discussed their study with any BPC individuals. i3 viewed its clients as Drs. Sprenger and Weidmann exclusively.

Not only was the i3 study's management delegated entirely to GDS, GDS also had an unusual amount of informational control over the study. Dr. Malik, chair of the TSC, had personally approved the study, but learned of the numerous communications among Drs. Weidmann, Sprenger, and i3 only *after* the Advisory Committee meeting. This surprised Dr. Malik, who had worked with Dr. Weidmann on other projects in which Dr. Weidmann regularly kept him abreast of project status. Dr. Weidmann's failure to do so for the i3 study was unusual and remains unexplained.

This isolation of the i3 study to two individuals resulted in the surprising fact that no one from BPC or Germany ever actually evaluated the Premier database's ability to do what i3 said it could do. At least one member of the TSC, Dr. MacCarthy, felt management should have ensured that the study's overseers performed extra due diligence on the Premier database, particularly given that BPC had previously considered using it for another study on Trasylo1, but had rejected it as inadequate. As it turned out, Dr. Weidmann told us GDS performed virtually no due diligence, choosing instead to rely entirely on i3's representation that the Premier database was an adequate data source for the study. The failure to resolve this issue before permitting GDS to proceed with the i3 study adversely impacted its priority within BPC.

### **III. The Preliminary Report – Who at Bayer Knew About the Preliminary Report, and Why Did Bayer Not Disclose Its Findings and Conclusions to FDA Before the Advisory Committee Meeting?**

#### **A. Only Dr. Weidmann and Dr. Sprenger knew of the Preliminary Report before the Advisory Committee meeting.**

Dr. Weidmann and Dr. Sprenger confirmed they were the only two people at Bayer who knew before the Advisory Committee meeting that the i3 study had yielded preliminary results. On Thursday, September 14, 2006, Dr. Walker emailed Drs. Sprenger and Weidmann a copy of the Preliminary Report, entitled “Mortality and Cardiovascular and Renal Outcomes in Recipients of Aprotinin, Aminocaproic Acid and Tranexamic Acid during CABG Surgery: Report on Computerized Inpatient Data from the Premier Perspective Comparative Database.”<sup>14</sup> Dr. Walker anticipated a call that day to discuss the Preliminary Report, but Sprenger postponed a meeting until the following Monday, September 18, because he and Dr. Weidmann were involved in a weekend-long meeting concerning the Bayer-Schering corporate integration.

#### **B. Dr. Weidmann and Dr. Sprenger did not tell anyone about the Preliminary Report because they had serious concerns about its scientific value.**

Drs. Weidmann and Sprenger said that when they reviewed the Preliminary Report, they quickly noticed discrepancies between the i3 study proposal and the study as actually conducted. They identified serious weaknesses in its methodology that caused them to doubt the scientific validity of the reported conclusions. According to Dr. Weidmann, because Dr. Malik had given GDS control over the i3 study, Dr. Weidmann did not feel obliged to inform Dr. Malik or colleagues in the United States about the study until GDS’s own concerns were addressed. Thus, he and Sprenger did not tell anyone else at Bayer about the Preliminary Report when they first received it.

Instead, Drs. Weidmann and Sprenger contacted Dr. Carlos Martinez, a scientific consultant to Bayer with training in epidemiology, to assist them in formulating questions about the Preliminary Report to send to i3. Martinez understood the turnaround time for his review was twenty-four hours, to permit GDS to send the questions to Dr. Walker before the Advisory Committee meeting.

Dr. Martinez’s review of the Preliminary Report reinforced Dr. Weidmann’s and Dr. Sprenger’s conclusion that the Preliminary Report suffered from serious problems. Dr. Martinez told us that, had he been peer-reviewing the Preliminary Report, he would not have recommended it for publication in its then-current form. The core problem with the Preliminary Report according to Dr. Martinez was that the Premier database was incapable of supporting the study originally proposed by i3. To Dr. Martinez, the database lacked sufficiently precise data, a deficiency which precluded reliable answers to the questions posed. Drs. Weidmann and

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<sup>14</sup> Dr. Seeger had first tried emailing the Preliminary Report on September 13, 2006, from his i3 email account, but i3 Drug Safety was experiencing technical problems with its email system. When Dr. Seeger did not receive a delivery confirmation for the September 13 email, Dr. Walker resent the Preliminary Report the following day using his personal email account.

Sprenger adopted Dr. Martinez’s analysis in full and, on September 18, emailed i3 eighteen questions and requests for clarification that fell into three main areas – outcomes, methods, and multivariate analysis.<sup>15</sup> Dr. Sprenger also asked Dr. Walker to tell him when i3 would send a “modified draft report.”

We were not asked to assess the scientific validity of Bayer’s criticisms of the Walker study, nor are we qualified to do so. However, the investigation was sufficient to conclude that Drs. Weidmann and Sprenger posed the eighteen questions in good faith scientific disagreement with the study’s methodology and analyses, not simply because they did not like the “answer” i3 had given them. Dr. Walker agreed that the questions were legitimate requests for clarification, although he did not consider the questions to be of a gravity that justified delaying reporting the outcome. Dr. Walker believes Dr. Weidmann and Dr. Sprenger should have given FDA the Preliminary Report along with the questions. Dr. Walker also maintained to us that the study was methodologically sound and the results sufficiently robust that the concerns Bayer raised would be unlikely to change the results.

The scientific validity of the study apparently remains in dispute.

**C. i3’s answers to the September 18 questions did not reach Drs. Weidmann and Sprenger until after the Advisory Committee meeting.**

Within hours of receiving Dr. Sprenger’s September 18 email with the eighteen questions and requests for clarification, Dr. Walker emailed back within hours to say that i3 was working on responses to Bayer’s comments.

The next day, September 19, Dr. Seeger tried to email Dr. Sprenger i3’s ten-page response. However, because of problems with i3’s email system, that email never reached Bayer’s email server.<sup>16</sup> That same day, Drs. Weidmann and Sprenger traveled to the United States for the final dress rehearsal of Bayer’s presentation and the Advisory Committee meeting. Dr. Sprenger told us he checked his email during the dress rehearsal, and during the Advisory Committee meeting itself, for any response from i3.

Dr. Weidmann told us that, had he received a response from i3 in time, he would have given the Preliminary Report, along with Bayer’s initial questions and i3’s response, over to FDA. The absence of the promised response from i3 prompted Dr. Weidmann to believe i3 might agree with the concerns reflected in the September 18 communication. Dr. Weidmann and Dr. Sprenger believed i3 might actually be revamping the study to address GDS’s comments. Because of this, Drs. Weidmann and Sprenger felt justified awaiting i3’s response before

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<sup>15</sup> During the investigation, Dr. Martinez confirmed that the three pages of comments provided to i3 were a copy of the comments he faxed to Drs. Weidmann and Sprenger on September 18.

<sup>16</sup> This was confirmed by an interview with BHC-AG’s computer specialist. He explained how Bayer’s email system records information about each external email sent to a BHC-AG email address, and provided a log of all emails sent to all of Dr. Weidmann and Dr. Sprenger’s Bayer email addresses in the relevant time period. The September 19 email from Dr. Seeger was not on the log. He confirmed “to a 99.9% certainty” that this email did not reach BHC-AG’s firewall. i3 confirmed email problems during this period.

disclosing the Preliminary Report to their BPC colleagues or to FDA before the Advisory Committee meeting.

Moreover, Dr. Weidmann recalled that during the Advisory Committee's consideration of the Mangano study on September 21, panel members outlined the criteria for a valid and reliable observational study. Dr. Weidmann recalled having felt reassured in his decision not to disclose the Preliminary Report because, in his view, the Preliminary Report failed the panel's standards.

In the end, both Drs. Weidmann and Sprenger persist in their belief that the Preliminary Report was of such little scientific value that their decision not to disclose the Preliminary Report was justified on scientific grounds. Dr. Weidmann, however, acknowledges a political misjudgment on his part in not informing his BPC colleagues.

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August 11, 2007

## APPENDIX

### TIMELINE OF EVENTS<sup>17</sup>

DATE (2006)	EVENT
January 20	The on-line edition of the journal <i>Transfusion</i> publishes “A Propensity Score Case-Control Comparison of Aprotinin and Tranexamic Acid in High-Transfusion-Risk Cardiac Surgery,” a report of an observational prospective study by Karkouti, <i>et al.</i> . The report indicates that patients receiving Trasylol experienced a higher rate of renal dysfunction compared to patients receiving tranexamic acid.
January 26	New England Journal of Medicine publishes “The Risk Associated with Aprotinin in Cardiac Surgery,” an observational study by Mangano, <i>et al.</i> . The article concludes aprotinin is associated with a higher risk of stroke, cardiovascular events, and renal failure compared to aminocaproic acid and tranexamic acid, the other drugs used to limit bleeding during or after coronary artery bypass graft (CABG) surgery.
February 1	Kuno Sprenger (copying Ernst Weidmann) emails Alexander Walker of i3 Drug Safety (“i3”) about i3 working on a retrospective safety study involving aprotinin, aminocaproic acid and tranexamic acid.
February 8	FDA issues a Public Health Advisory to notify healthcare professionals and consumers about the results of the Mangano and Karkouti studies. FDA also indicates an intent to hold an advisory committee meeting on Trasylol.
February 9	Walker emails i3’s initial concept letter for a retrospective data analysis to Sprenger.
February 16	At Sprenger’s request, Walker emails a fuller concept letter, which Sprenger forwards to Weidmann on February 17.
February 20	The German domestic subsidiary of BHC-AG submits a Stufenplan (a “Step Plan” outlining the actions the drug sponsor intends to take) to the German pharmaceutical regulatory agency (Bundesinstitut für Arzneimittel und Medizinprodukte, or BfArM). It mentions that Bayer may embark on a pharmaco-epidemiological study using a database from the United States.
February 22	Bayer submits to FDA a summary of the clinical safety of aprotinin in CABG patients in response to the Mangano and Karkouti articles.

<sup>17</sup> For brevity, this chart does not provide a complete list of recipients copied on each email, and refers to individuals by last name.

DATE (2006)	EVENT
February 23	Sprenger emails Walker (copying Weidmann) and poses questions about the extended concept letter. Sprenger notes that Bayer is expecting an Advisory Committee meeting in the late summer time and asks Walker to present the results.
February 28	Bayer issues a “Dear Healthcare Provider” letter based on FDA’s February 8 Public Health Advisory.
March 3	John Seeger of i3 emails a “more formal” study proposal to Sprenger and Weidmann. The proposal states that i3 will deliver to Bayer preliminary results based solely on information in the Premier database within 6 months of contract execution.
March 18	At the suggestion of Kemal Malik, Bayer’s Head of Global Development, Weidmann (copying Sprenger and Walker) emails the i3 proposal to Samy Suissa, a professor of epidemiology at McGill University and consultant to Bayer. Malik suggested Suissa as an neutral outside expert to provide an independent assessment of the i3 study proposal, to resolve disagreement among Trasylol Steering Committee (“TSC”) members.
March 28	Suissa emails comments to Weidmann (copying Sprenger and Walker). Suissa reviews the i3 proposal, but not reviewed the database. Although Suissa raises some questions about the level of detail in the database and how i3 plans to account for potential confounding factors, he has an overall positive reaction.
April 4	Walker, in an email to Sprenger and Weidmann, responds to Suissa’s questions about statistical methods, but not to questions concerning the adequacy of the data source.
May 17	Weidmann emails Malik asking that the TSC discuss the i3 proposal at the TSC’s upcoming meeting in light of Suissa’s positive review and Weidmann’s desire to proceed with the study.
June 1	Malik gives his official approval to proceed with the i3 study.
June 2	Sprenger informs Walker (copying Weidmann) of Bayer’s approval of the study and that Bayer would like Walker to perform the study in time to meet the deadline of the September 21 Advisory Committee meeting.
June 9	Seeger emails Sprenger (copying Walker) a draft contract and notes that timelines for delivery of results have been compressed to accommodate Bayer’s request.
June 19	Sprenger emails Seeger (copying Walker and Weidmann) a signed copy of

DATE (2006)	EVENT
	<p>the Services Agreement. Exhibit A to the Services Agreement provides for preliminary results based exclusively on electronic data from the Premier database within 3 months of the executed contract. A final report, scheduled for delivery 4 months after the Preliminary Report, is to include “supplemental data provided by medical record review and sensitivity analyses.” The cost of the study is \$700,000, to be paid in 5 installments.</p>
June 28	<p>Telephone conference with FDA. Scheeren believes Bayer committed to inform FDA of the i3 study during this call, but FDA ends the call abruptly before the i3 study comes up.</p>
July 13	<p>Sprenger emails Walker again asking whether Walker would be willing to present the study data at the Advisory Committee meeting and informs Walker that the briefing packet to FDA is due August 18.</p>
July 16	<p>Bayer prepares for the July 17 face-to-face meeting with FDA. Among the Bayer attendees are Cyrus, Heller, MacCarthy, Nadel, Rozycki, Scheeren, Shah, Sprenger, Taylor, and Van Veenhuizen.</p> <p>Accounts vary, but it appears that Sprenger gave the Bayer group a verbal overview of the i3 study. Sprenger claimed he told Scheeren and MacCarthy that preliminary results would be ready for the Advisory Committee. Neither recalled this.</p> <p>According to MacCarthy, the group decides to inform FDA about the i3 study at the meeting. Several present recall Scheeren telling Sprenger to be prepared to discuss the i3 study when it comes up.</p>
July 17	<p>FDA-Bayer meeting in Silver Spring, Maryland. Bayer does not raise the i3 study.</p> <p>Walker emails Sprenger that he and Seeger would be happy to present results at the Advisory Committee meeting. No one at BPC recalls any discussion or consideration of allotting time at the Advisory Committee meeting for such a presentation.</p> <p>Seeger emails Sprenger and Walker explaining that the i3 study results will not be available in time for the briefing package deadline (August 18), but suggests that Sprenger provide a description of the study for the briefing package. (No such description is included.)</p>
July 20	<p>Shah circulates the i3 study proposal to the TSC. (The email includes a string of several prior emails, most of which were redacted when provided during the investigation.)</p>

DATE (2006)	EVENT
July 21	Sprenger emails i3 proposal to MacCarthy (copying Weidmann).
July 22	Bayer holds its first mock panel in New York City to prepare for the Advisory Committee meeting, attended by about 40 people. Neither Sprenger nor Weidmann attends. Accounts vary, but most central participants do not recall any mention of the i3 study at this meeting.
August 17	<p>Bayer submits its briefing document and supporting materials to FDA for the Advisory Committee meeting.</p> <p>Seeger emails Sprenger that i3 is on track to meet the contract's schedule for delivering preliminary results. In the same email, Seeger invites Sprenger and Weidmann to meet Seeger, Walker, and Sebastian Schneeweiss (an i3 contractor managing the i3 study) at the upcoming International Society for Pharmacoepidemiology ("ISPE") conference in Lisbon (August 24-27).</p>
August 19	Bayer conducts its second mock panel in New York City. Sprenger is present; Weidmann is not. Sprenger remembered mentioning the status of the i3 study to some people at some point during the pre-meeting to this mock panel, including Scheeren and MacCarthy. By contrast, several attendees distinctly recalled Sprenger reporting that no results from the study would be available before the Advisory Committee meeting.
August 23	Sprenger emails Seeger proposing that i3 meet at the ISPE conference with Tomasz Dyszynski, International Drug Safety Manager for Aprotinin.
August 26	Dyszynski and Conny Berlin, an employee in Bayer's Department of Integrated Analysis, meet with i3. Notes taken by Dyszynski at this meeting identify some problems later highlighted in GDS's questions to i3 concerning the Preliminary Report; however, neither Weidmann nor Sprenger recalled Dyszynski reporting these issues in detail when Dyszynski briefed them on the meeting.
September 6	After hearing from Dyszynski that preliminary results will be available from the i3 study the first week in September, Sprenger emails Walker (copying Weidmann) proposing a meeting or conference call to discuss preliminary results.

<b>DATE (2006)</b>	<b>EVENT</b>
September 7	<p>Walker emails Sprenger and Weidmann that i3 is ready to give Sprenger a summary of findings.</p> <p>Weidmann sends an email containing the March 3 i3 proposal to MacCarthy, Scheeren, and Tucker.</p> <p>Sprenger separately re-forwards his July 21 email with the i3 proposal to MacCarthy, Scheeren, and Tucker.</p>
September 8	<p>Walker emails Sprenger (copying Weidmann) and withdraws his September 7 offer to give Sprenger a preview of the findings, saying to do so would be premature.</p>
September 9	<p>Bayer holds its third mock panel in New York City, attended by about 35 people. Sprenger is present; Weidmann is not.</p> <p>Sprenger responds to Walker's September 7 email, noting that he (Sprenger) is busy with Bayer's mock panel. Sprenger proposes a conference call for the following Monday (September 11).</p>
September 13	<p>Seeger emails Sprenger the Preliminary Report. Sprenger apparently does not receive the report on that day because of problems with i3's email system.</p>
September 14	<p>Using his personal email account, Walker resends the Preliminary Report to Sprenger (copying Weidmann). Sprenger and Weidmann confirm receipt.</p>
September 15-18	<p>Sprenger and Weidmann ask Carlos Martinez to review the Preliminary Report.</p>
September 18	<p>Sprenger emails i3 three pages of eighteen comments and questions about the Preliminary Report.</p> <p>Later that day, Walker responds via email that i3 is working on responses to the eighteen questions and that i3 will contact Sprenger and Weidmann as soon as they are ready.</p>

DATE (2006)	EVENT
September 19	<p>Seeger attempts to email i3's 10-page response to Weidmann and Sprenger. However, Seeger's email never reaches Bayer's system because i3 continues to have problems with its email system. Both i3 and Sprenger/Weidmann are unaware that Seeger's email transmission fails.</p> <p>Max Wegner, BHC-AG's regulatory director, recalled asking Weidmann if there is anything new from GDS while on the plane from Germany to US for the Advisory Committee, Max Wegner. Weidmann says no. (Weidmann claimed not to recall this conversation.)</p>
September 20	<p>Bayer holds dress rehearsal for Advisory Committee meeting in Bethesda, Maryland. Both Weidmann and Sprenger are present. According to several witnesses, Scheeren poses a question about the status of the i3 study to Weidmann. No BPC witnesses recalled Weidmann disclosing that GDS had received the i3 Preliminary Report a week earlier. Weidmann and Sprenger both denied that there was any discussion of the i3 study at the dress rehearsal, other than a private conversation between them regarding whether i3 had responded to their 18 questions.</p>
September 21	<p>Meeting of FDA's Cardiovascular and Renal Drugs Advisory Committee occurs in Bethesda Maryland. No one from Bayer mentions the i3 study nor its preliminary results and conclusions.</p>
September 22	<p>Seeger emails Sprenger seeking confirmation that Sprenger received i3's September 19 responses to Bayer's questions. This email arrives in Sprenger's in-box late Friday evening German time.</p> <p>Walker emails Sprenger (copying Weidmann) asking why the i3 study was not mentioned at the Advisory Committee.</p>
September 25	<p>This appears to be the day Sprenger opens i3's email containing i3's responses to the three pages of questions sent on September 18. Sprenger's administrative assistant forwards Seeger's email to Weidmann.</p> <p>Walker, Seeger, Sprenger and Weidmann hold a teleconference at 10:00 am US time.</p> <p>Sprenger emails Suissa a copy of the i3 proposal, the Preliminary Report, Bayer's questions and i3's responses. Sprenger also confirms with Suissa a conference call scheduled for the next day.</p>
September 26	<p>Weidmann emails Walker explaining that Bayer did not receive i3's answers to its questions until September 22, and that they wanted Suissa to review the</p>

<b>DATE (2006)</b>	<b>EVENT</b>
	<p>study before any disclosure to FDA.</p> <p>Walker responds via email his view that the Preliminary Report has implications for public health and must be communicated to FDA. Walker requests that Bayer submit the report to FDA by September 28.</p> <p>Sprenger (copying Weidmann) emails Suissa, attaching comments in response to i3's September 19/22 answers.</p>
September 27	Bayer informs FDA about the study within 3 hours of Rozycki receiving the i3 Preliminary Report by email.
October 13	Bayer announces that it has retained Fred Fielding, then of the Washington, DC law firm Wiley Rein & Fielding, to conduct an independent investigation into the Trasylol matter.
January/February 2007	On January 8, 2007, Fielding is named White House Counsel by President Bush. On February 7, 2007, Bayer retains William W. Taylor III of the Washington, DC law firm Zuckerman Spaeder LLP to conduct the independent Trasylol investigation.