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Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Program Enforcement Branch I (HFZ-311)
2098 Gaither Road
Rockville, Maryland 20850

Attention: Doreen Kezer, MSN, Consumer Safety Officer

Dear Ms. Kezer:

This letter reports information obtained from an investigation by the Alfred I. duPont Hospital for Children's Institutional Review Board into the use of the Cheatham Platinum covered stent ("the CP stent") at the Hospital.[1] The Hospital determined that Dr. John D. Murphy, along with other physicians, acquired and used the CP stent as part of an innovative approach to treatment of children with congenital heart disease. In doing so, Dr. Murphy and other physicians did not comply with Hospital and IRB policies and procedures regarding patient protection procedures and the use of medical devices. The Hospital also determined that several complaints by the parents of Patient #7 were poorly handled. As reflected below, the Hospital and its IRB are committed to a comprehensive corrective action plan to ensure these problems do not reoccur.

I. ACQUISITION AND USE OF THE STENT

A. FDA Classification of the Stent

The CP stent is manufactured by NuMed, Inc. (NuMed), a medical device manufacturer based in Hopkinton, NY. Based on its investigation, the Hospital believes that the CP stent was never approved under any status by the Food and Drug Administration (FDA). Nonetheless, NuMed commercially

[1] Although the IRB initiated the investigation, both the Hospital and the IRB join to report the results and the joint corrective action plan. Therefore, we will refer to both the Hospital and the IRB as 'the Hospital."

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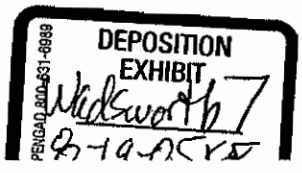

distributed CP stents to Dr. John Murphy at the Nemours Cardiac Center without clearance or approval from the FDA. Consequently, the Hospital understands that the FDA believes NuMed distributed adulterated devices in violation of the Food, Drug and Cosmetic Act. The Hospital now knows that NuMed applied unsuccessfully for a Humanitarian Device Exemption in 2000-01 and applied for an Investigational Device Exemption in August 2003.

On March 31, 2000, NuMed applied to the FDA to have the CP stent classified as a Humanitarian Use Device ("HUD") under section 520(m) of the Food, Drug and Cosmetic Act. **Tab 1.** On May 10, 2000, the FDA informed NuMed that the CP stent qualified as an HUD for "treatment of native and/or recurrent coarctation of the aorta in infants and children with congenital heart disease." But there is no evidence that NuMed ever sought FDA approval for use of the device for Fontan completion, which is a different procedure.

On June 12, 2000, NuMed applied to the FDA Center for Devices and Radiological Health (CDRH) for a Humanitarian Device Exemption (HDE) for the CP stent. The FDA immediately informed NuMed of the materials required for a complete HDE application and instructed NuMed to submit additional materials, if necessary, as amendments to the original HDE application.

On July 5, 2000, the FDA informed NuMed by letter that the CDRH had found NuMed's original HDE application for the CP stent deficient because of lack of information about NuMed's manufacturing capabilities. **Tab 2.** The FDA stated its intention to conduct an inspection of the NuMed facility to determine whether NuMed was capable of manufacturing the CP stent in accordance with the requirements of 21 CFR § 820. The Hospital does not know whether the FDA ever conducted that inspection.

On July 14, 2000, the FDA notified NuMed that the CDRH found the HDE application for the CP stent deficient, and that the FDA would not file the application until NuMed remedied all listed deficiencies. **Tab 3.** NuMed submitted amendments to the CP stent HDE application on July 18, 2000, November 3, 2000 and November 9, 2000. One month after the last amendment, on December 8, 2000, the FDA informed NuMed that its CP stent HDE application was sufficiently complete to undergo substantive review, and it deemed the HDE application filed as of November 9, 2000. **Tab 4.**

On January 23, 2001, the FDA completed its initial scientific review of the HDE application and informed NuMed that "the HDE lacks the information needed to determine if the device meets the statutory criteria for approval." **Tab 5.** In its January 23, 2001 letter, the FDA listed the deficiencies in the HDE application that NuMed would have to remedy to obtain an HDE for the CP stent.

According to information obtained by counsel, the Hospital believes that NuMed met with FDA representatives to discuss the HDE application on March 16, 2001. The NuMed meeting minutes state that Donna Buckley of the FDA advised NuMed to withdraw the HDE application and instead file an Investigational Device Exemption (IDE) application for the CP stent. That same day, NuMed wrote a letter to the FDA withdrawing its HDE application and informing the FDA of NuMed's intention to file an IDE application for the CP stent. **Tab 6.**

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The Hospital believes that NuMed took no further action to obtain approval for the CP stent until May 2003.[2]

Based on its investigation, the Hospital understands that both bare and covered CP stents were commercially distributed without clearance to Dr. John Cheatham, Dr. Ziyad Hijazi, and other physicians from as early as 1998. **Tab 8.** Approximately 44 patients had the CP stent implanted for a variety of medical indications, including the Fontan completion, before Dr. Murphy first used the stent. Dr. Murphy stated that he became aware of the use and availability of the CP stent in approximately January-May 2001. He first ordered a CP stent in January 2002.

Dr. Murphy stated that he did not know the regulatory history of the NuMed covered stent, including NuMed's unsuccessful efforts to obtain clearance or approval from the FDA. As discussed below, Dr. Murphy stated that he did not know or inquire about the regulatory history of the device before he first obtained a covered stent from NuMed. Rather, he stated that he followed NuMed's instructions on how to acquire the stent.

According to information obtained by counsel, the Hospital believes that NuMed and the FDA met again on June 17, 2003, and at that meeting NuMed President Allen Tower stated that the CP stent had been distributed as a "custom use" device.[3] At that meeting a representative of the FDA advised NuMed, Dr. Cheatham and Dr. Hijazi that the CP stent was not a "custom use device."

After initiating a product recall, NuMed applied for an IDE for the CP stent. On August 7, 2003, the FDA received NuMed's IDE application. **Tab 10.** On September 3, 2003, the FDA disapproved NuMed's IDE application for the CP stent and indicated that it would not further consider the CP stent IDE application until it received significant information on all of the patients who had received the stent, as well as other manufacturing information. **Tab 11.** To the Hospital's knowledge, NuMed submitted additional material supporting the CP stent IDE application on several occasions prior to January 31, 2004, and the FDA has not completed its evaluation of the CP stent IDE application.

B. The Use of the CP Stent at the Hospital

The Norwood procedure is a three-step surgical therapy, performed on infants for the correction of Hypoplastic Left Heart Syndrome (HLHS). HLHS is a rare congenital heart defect that is uniformly fatal unless corrected by the Fontan completion. Drs. John D. Murphy and William I. Norwood endorsed the use of the CP stent for nonsurgical completion of the

[2] On March 27, 2003, NuMed revised its original HUD request for the indication of "treatment of native and/or recurrent coarctation of the aorta." **Tab 7.**

[3] The Hospital also understands that Dr. Ziyad M. Hijazi and Dr. John P. Cheatham attended the June 17, 2003 meeting with the FDA. Dr. Hijazi published an article in August 2003, in which he stated that he obtained the CP stent from NuMed as a "custom ordered/made device." Hijazi, Z., "Catheter Intervention for Adult Aortic Coarctation: Be Very Careful," Catheterization and Cardiovascular Intervention, 59:536-537 (2003). **Tab 9.** The Hospital does not know whether Dr. Hijazi submitted his article for publication prior to the June 17, 2003 meeting.

Fontan procedure in the Nemours Cardiac Center, believing that transcatheter insertion of a CP stent was in the patient's best interest because it avoided a third surgical operation.[4]

Dr. Murphy stated that he learned at a professional conference at some point between January 2001 and May 2001 that the CP stent was available in the United States. He stated that he passed this information along to Dr. Norwood and other physicians in the Nemours Cardiac Center, and together they decided to complete the Fontan procedure with the CP stent using a catheterization procedure.

Dr. Murphy stated that he was generally aware that Dr. Cheatham and Dr. Hijazi had used the CP stent prior to 2002. Had Dr. Murphy examined the medical literature on the CP stent, he would have determined that Dr. Cheatham had used the CP stent on numerous occasions after "informed consent and IRB/Ethical Committee approval;"[5] or that the NuMed CP stent was "currently under investigation with promising results."[6] In fact, in May 2001, Dr. Cheatham published an article suggesting that the CP stent had been the subject of clinical trials for coarctation of the aorta, but that certain questions would have to be answered before FDA approval of the device as an HUD.[7] **Tab 12.**

Some time before his first use of the CP stent for transcatheter completion of the Fontan procedure on April 30, 2002, Dr. Murphy spoke informally with Dr. Rob Locke, the vice-chair of the Hospital's IRB, about whether use of the CP stent required IRB oversight. There is no written record of the conversation. Dr. Murphy stated that he told Dr. Locke that the stent was unapproved. He further stated that Dr. Locke told him that no IRB oversight was required so long as Dr. Murphy was using the CP stent for treatment, not research – that is, so long as he was making a clinical determination that the CP stent was an appropriate therapy, rather than "randomizing" patients to the CP stent or the conventional surgical completion of the Fontan procedure. Dr. Locke stated that he vaguely recalled this conversation, but said that he understood Dr. Murphy to be asking about the off-label use of an approved device for treatment in rare cases, rather than research or the use of an unapproved device.

Dr. Murphy stated that he and other physicians never randomized patients between the surgical completion and transcatheter completion of the Fontan procedure with the CP stent. Rather, Dr. Murphy stated that he and other physicians made individual treatment

[4] From 1998, when the Nemours Cardiac Center (NCC) was opened, until February 19, 2004, Dr. Norwood served as the Director and Chief Executive of the NCC. Dr. Murphy served as the Chief of Cardiology during that same period of time. The NCC was created as an independent operating division of the Nemours Foundation and it operated as an autonomous entity under the direction of Dr. Norwood.

[5] Cheatham, J. et al., "Initial Experience Using the NuMED Cheatham Platinum (CP) Stent and a New Balloon Delivery Catheter in Children and Adults with Congenital Heart Disease." Catheterization and Cardiovascular Interventions 47:122 (1999).

[6] Cheatham, J., "A Tragedy During Palmaz Stent Implant for SVC Syndrome: Was it the Stent or was it the Balloon Delivery System?" Catheterization and Cardiovascular Interventions 49:163-166 (2000).

[7] Cheatham, J., "Stenting of Coarctation of the Aorta." Catheterization and Cardiovascular Interventions 54:112-125 (2001).

decisions for each HLHS patient and determined in each case that the CP stent was an appropriate therapy for the patient's condition.[8]

Dr. Murphy and other physicians used an informed consent document provided by the manufacturer. The NuMed informed consent document stated that the CP stent "was not approved by the Food and Drug Administration (FDA)," yet the document also described the device as "investigational." The NuMed consent form was not submitted to the IRB, and therefore not reviewed or approved by the IRB as required by Hospital policy.[9]

On February 21, 2003, about nine months after the first use of the stent, Dr. Murphy and other physicians submitted to the IRB a request for expedited approval of a medical records review and the proposed protocol for conducting the review. **Tab 13.** The protocol, entitled "Interventional Fontan Completion for HLHS," stated that the purpose of the review was to "report the results of transcatheter completion of the Fontan procedure performed in the cardiac catheterization lab." The proposed cohort for the study was "all eleven patients who have undergone the Fontan procedure in the cardiac catheterization lab between January 2002 and January 2003." The stated method for the study was data collection from a retrospective chart review. Neither the request for approval nor the protocol specifically mentions the use of a stent or any other device in the transcatheter completion of the Fontan procedure. On March 4, 2003, the IRB granted expedited approval for the medical records review.

In May 2003, Drs. Murphy, Murdison, Nehgme, Pizarro and Norwood submitted an abstract entitled "Catheter Facilitated Completion of the Fontan Procedure" to the medical journal *Circulation*. *Circulation* published the abstract on October 28, 2003. **Tab 14.** The *Circulation* abstract was based on the medical records review data. Dr. Murphy also presented on this topic at both the Nemours Research Symposium on June 3, 2003, and at the American Heart Association Conference in Orlando, Florida on or about November 11, 2003. **Tab 15.** The abstract and presentations described the use of the NuMed CP stent in the "Interventional Fontan Completion for HLHS."

C. Research Versus the Practice of Medicine

The Hospital understands that Dr. Murphy did not use the CP stent in the context of traditional research. Research is defined as a "systematic investigation, including research, development, testing and evaluation, designed to develop or contribute to generalizable knowledge." 45 CFR § 46.102(d). NuMed did not distribute the CP stent as if it were an IDE and thus subject to a clinical study protocol. Here, the hallmarks of a "systematic investigation"

[8] Hospital records show that after April 2002, nearly all patients requiring the third stage of the Fontan procedure had the CP stent implanted in the catheterization laboratory, rather than undergo the surgical procedure.

[9] Hospital policy requires IRB review of informed consent documents for investigational devices. The NuMed informed consent document was reviewed by the FDA in August-September 2003, and as a result of the FDA review, the description was changed to "compassionate use device" rather than "investigational." The FDA made other significant changes to the informed consent document for prospective compassionate use cases. The IRB was not aware of the specific compassionate use cases and was not provided an opportunity to review or approve the informed consent document, as required by Hospital policy.

...iat define research were not present. There was no clinical protocol; no principal investigator; no systematic effort to collect and report data; no preparation of case report forms; no IRB oversight; no adverse event reporting protocol.

The practice of medicine is not regulated by the FDA, so long as the health care practitioner prescribes or administers any legally marketed device to a patient for any condition or disease within a health care practitioner – patient relationship. 21 U.S.C. § 396. Here, Dr. Murphy obtained a device that was not "legally marketed" by NuMed. Nonetheless, the Hospital understands that Dr. Murphy used the device in the practice of medicine – that is, to treat patients in need of a Fontan completion procedure.

Dr. Murphy's actions did not squarely fit into the category of research or the practice of medicine. While Dr. Murphy used the CP stent without knowledge of the regulatory status of the unapproved device, his intent in using it appeared to be the clinical care of his patients. Yet, while there was no "systematic investigation" or other hallmarks of "research," Dr. Murphy and other physicians did use an "investigational" informed consent form and did present and publish the clinical outcomes of CP stent patients, which could give the appearance that the use of the CP stent was part of research. Hospital policy states that the IRB is responsible for making the final determination that a project is or is not research. Here, Dr. Murphy did not properly notify the IRB about his use of an unapproved medical device, which prevented the IRB from exercising its oversight authority.

On February 12, 2004, Commander Despins (FDA Auditor) issued his stablishment Inspection Report (EIR), the product of his audit of the IRB and of the use of the CP stent at the Hospital. His audit concluded that the IRB's procedures for review of informed consent documents and research protocols were appropriate. Tab 16. Commander Despins concluded that "it was not a violation of the regulations for an individual to receive these stents, [for] which the manufacturer had no HUD/HDE/IDE from the FDA."

Regardless, the Hospital remains concerned about physicians using unapproved medical devices, like the CP stent, in innovative clinical care. The Hospital has very serious concerns that Dr. Murphy did not first seek review by the IRB and obtain assurance from the manufacturer that the device was legally marketed and approved for distribution. Regardless of this distinction between research and the practice of medicine, the Hospital intends to take corrective action to ensure that devices distributed without FDA clearance do not escape IRB oversight. Moreover, the Hospital will enhance its existing policies to ensure that the determination of whether a particular activity constitutes research rests solely with the IRB.

D. Dr. Murphy's Understanding and Use of the Stent

1. Dr. Murphy understood that the CP stent was not approved by the FDA.

During the investigation, Dr. Murphy stated that he understood that the CP stent was unapproved by the FDA. Dr. Murphy also indicated that he did not believe the CP stent was approved for use under an HDE, IDE or any other exemption. He said that while he knew the

stent was unapproved, he relied on the assurances of NuMed that the stent was available in the United States and obtainable by prescription for the treatment of individual patients.[10]

Dr. Murphy did send prescriptions to NuMed, but it is not clear what standard NuMed used to ship the unapproved devices. On January 22, 2002, three months before his first use of the CP stent, Dr. Murphy faxed a handwritten order for the stent to Allen Tower of NuMed requesting a 3.5 cm CP stent. This order was not, to the Hospital's knowledge, accompanied by a written prescription. NuMed shipped Dr. Murphy the requested catheter and stent on January 23, 2002. **Tab 17.** Dr. Murphy also faxed handwritten orders for stents to NuMed on May 2, 2002 and May 22, 2002. **Tab 18.** To the Hospital's knowledge, neither request was accompanied by a written prescription.

Upon receipt of Dr. Murphy's May 22, 2002 purchase order, NuMed requested that Dr. Murphy fill out the "Request for Emergency Use of CP Stent" form. **Tab 19.** The form detailed the circumstances and procedures for emergency use of an unapproved device, including notice to the IRB. Dr. Murphy signed and returned the form to NuMed. To the Hospital's knowledge, Dr. Murphy did not use the device in conformance with the emergency use requirements provided by NuMed.

On June 12, 2002, Dr. Murphy faxed another request to NuMed, and received in return a faxed request to provide a prescription and a completed emergency use form. **Tab 20.** This fax from NuMed also included a copy of a guidance document governing the emergency use of unapproved medical devices. As with the May 22, 2002 request for a signed emergency use form, Dr. Murphy signed the June 12, 2002 emergency use form, and once again, did not perform the actions listed on the NuMed form as required for emergency use of an unapproved device.

On July 12, 2002, Dr. Murphy submitted to NuMed a typewritten form letter on Hospital stationery, requesting CP stents of various sizes. **Tab 21.** For the first time known to the Hospital, he included prescriptions with his stent order. Dr. Murphy used this letter as a template for the orders that he submitted on September 9, 2002, December 9, 2002, March 19, 2003, April 14, 2003, and June 12, 2003. Dr. Murphy included prescriptions with all of those orders..

On June 26, 2003, Dr. Murphy received a letter from NuMed, titled "**URGENT MEDICAL DEVICE RECALL**." This letter informed Dr. Murphy that the CP stent was not FDA-approved, asked that Dr. Murphy account for the CP stents that he had ordered from NuMed, and advised Dr. Murphy that the covered CP stent was not to be used except in emergency use and compassionate use cases. **Tab 22.** During the investigation, Dr. Murphy confirmed his understanding that after June 26, 2003, the CP stent could only be used in emergency use and pre-approved compassionate use cases.

[10] Dr. Murphy had experience as a clinical investigator in unrelated, but approved, clinical studies.

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2. Dr. Murphy received the CP stent after submitting purchase orders and prescriptions to NuMed.

Based on its investigation, the Hospital determined that Dr. Murphy usually obtained the CP stent by following the process described to him by NuMed: he wrote a patient-specific prescription for the CP stent, which he then faxed to NuMed along with a handwritten or typed purchase order. With the exception of two early stent orders, NuMed did not require certification from Dr. Murphy that the stent was ordered for emergency use.

From April 2002 to June 26, 2003, Dr. Murphy did not place orders and submit prescriptions for stents so that he could use the stents he received in the patients for whom he was ostensibly prescribing the stent. Instead, he wrote prescriptions after each patient's procedure as were necessary to restock his supply of CP stents.

Within the Hospital, after Dr. Murphy submitted a purchase order and prescription to NuMed, Cardiac Center staff would obtain a purchase order number from the Hospital's Materials Management Department. They would then phone NuMed and provide the purchase order number so that NuMed could include the purchase order number in the routing instructions for shipment of the CP stents. The Materials Management Department played no role in determining whether the CP stent was an approved device or whether NuMed was a device manufacturer with whom the Hospital typically conducted business. After receiving a purchase order and prescription, NuMed would send the CP stents to the Nemours Cardiac Center by Priority Overnight Federal Express to Dr. Murphy's attention in the Nemours Cardiac Center.

E. CP Stent Implantation Prior to Recall

In October 2003, Dr. Murphy and Cardiac Center staff provided patient records to NuMed and the FDA regarding CP stent patients. A brief summary of those patients is provided below:[11]

Patient #1

Dr. Murphy first used the CP stent for the completion of the Fontan procedure on April 30, 2002, in Patient #1.[12] Patient #1's parents signed a NuMed consent form. They also signed a Nemours consent form for "[t]ranscatheter placement of intravascular stent: covered stent placement for completion of Fontan." Patient #1 was doing well during the three month, six month and one year follow-up visits with the Nemours Cardiac Center. The Nemours Cardiac Center evaluated Patient #1 on May 5, 2003. During its investigation, the Hospital found no evidence that suggests that Patient #1 received the CP stent on an emergency use basis.

[11] These brief patient summaries are based solely on records requested by and provided to NuMed in October 2003. As a result, this Report does not attempt to summarize the entire medical history of these patients.

[12] The "Stent Information" form that was provided to NuMed misstates the date of procedure as being May 1, 2002. Tab 23.

Patient #2

On June 11, 2002, Dr. Murphy performed his second transcatheter completion of the Fontan procedure. Patient #2's parents signed a NuMed consent form regarding the use of the CP stent on the day of Patient #2's procedure. They also signed a Nemours consent form, which indicates that on June 11, 2002, Patient #2 was to undergo "[t]ranscatheter placement of intravascular stent: [e]valuation, possible stent completion of Fontan." Patient #2 received a CP stent on June 11, 2002 and showed no signs of complications at the three month, six month and one year follow-up visits with the Nemours Cardiac Center. The Nemours Cardiac Center evaluated Patient #2 on August 5, 2003. The Hospital found no evidence that suggests that Patient #2 received the CP stent on an emergency basis.

Patient #3

On June 20, 2002, Dr. Murphy implanted a CP stent in Patient #3 to complete the Fontan procedure. Patient #3's parents signed a NuMed consent form and a Nemours consent form for "[o]ther: possible stent completion of cavopulmonary connection." After the procedure, which was performed by Drs. Murphy and Murdison, the physicians detected "a small residual right-to-left shunt" or possible leak through a tear in the CP stent membrane. On July 3, 2002, Patient #3's parents signed another set of consent forms and Dr. Murphy implanted a second stent in Patient #3 to remedy the shunting. The second procedure was a success, and Patient #3 was doing well at the three month, six month and one year follow-up visits with the Nemours Cardiac Center. The Nemours Cardiac Center evaluated Patient #3 on April 24, 2003. Dr. Murphy did not appear to use these stents on an emergency basis.

Patient #4

On July 8, 2002, Dr. Murphy implanted a CP stent in Patient #4 during a transcatheter completion of the Fontan procedure. On the day of the procedure, one of Patient #4's parents signed a Nemours consent form for "[o]ther: possible transcatheter Fontan completion." Dr. Deborah Davis (NCC physician) signed the Nemours consent form as the physician who provided the informed consent information. The Hospital has no record that Patient #4's parents signed the NuMed consent form at the time of Patient #4's procedure. In October 2003, Dr. Murdison and cardiac staff members submitted to NuMed and the FDA a NuMed informed consent document signed by Patient #4's parent, Dore Klenk (Cardiac Center technician) and Dr. Murphy. Although signed and dated in October 2003, the document reflects a date of "7/8/2002," the date of Patient #4's procedure. **Tab 24**. This issue is discussed more fully below. The July 8, 2002 procedure for Patient #4 was not without complications. After the procedure, Patient #4 showed signs of possible displacement of the CP stent. On July 9, 2002, Dr. Murphy implanted a second stent in Patient #4. Patient #4's parents signed only the Nemours consent form for this second procedure. Patient #4 was doing well at the three month, six month and one year follow-up visits with the Cardiac Center. The Nemours Cardiac Center evaluated Patient #4 on August 21, 2003.

Patient #5

On August 5, 2002, Dr. Murphy implanted a CP stent in Patient #5 to complete the Fontan procedure. Patient #5's parents signed both the NuMed consent form and a Nemours consent form for "transcatheter placement of intravascular stent: Fontan [c]ompletion." There were no complications. On May 6, 2003, during Patient #5's follow-up visit with the Nemours Cardiac Center, Patient #5 had minor insufficiency in the flow from the inferior vena cava through the stent to the pulmonary arteries.

Patient #6

On September 5, 2002, Dr. Murphy implanted two CP stents in Patient #6 to complete the Fontan procedure. Patient #6's parents signed both the NuMed consent form and a Nemours consent form for "[t]ranscatheter placement of intravascular stent: stent completion of Fontan." Patient #6 received two stents, the second of which was placed to prevent right-to-left shunting. At a follow-up visit with the Nemours Cardiac Center on March 14, 2003, Patient #6 showed no signs of complications and was doing well.

Patient #7

On October 14, 2002, Dr. Murphy implanted a CP stent in Patient #7 to complete the Fontan procedure. There were no complications. On October 6, 2003, Dr. Kenneth Murdison sent a letter to NuMed indicating that the Nemours Cardiac Center was unable to locate Patient #7's medical records and therefore could not send Patient #7's consent forms in response to NuMed's request. **Tab 25.** This issue is discussed more fully below. Hospital records reflect that patient #7's father signed a Nemours consent form for "covered stent completion of cavopulmonary connection."

Patient #8

On October 21, 2002, Dr. Murphy completed the Fontan procedure in Patient #8. Patient #8's parents signed the NuMed consent form and a Nemours consent form for "transcatheter placement of intravascular stent: Fontan completion." The CP stent implantation was generally a success, but Patient #8 suffered chronic right pleural effusions after the surgery. Patient #8 underwent thoracentesis in March and April 2003 to correct the pleural effusions. Patient #8's last visit with the Nemours Cardiac Center was on April 14, 2003.

Patient #9

On January 13, 2003, Dr. Murphy completed the Fontan procedure with the CP stent in Patient #9. Patient #9's parents signed the NuMed consent form and a Nemours consent form for "possible completion of cavopulmonary connection." During the procedure, the first CP stent tilted medially during placement. Dr. Murphy deployed a second CP stent and completed the Fontan procedure. After the procedure, physicians in the Nemours Cardiac Center detected some minor right-to-left shunting of the CP stents. Dr. Gidding discharged Patient #9 on January 27, 2003, at which time Patient #9 was tolerating the procedure well.

Patient #10

On January 20, 2003, Dr. Murphy implanted a CP stent in Patient #10, for repair of a right atrial baffle leak. This procedure was not a Fontan completion. Patient #10's mother executed a NuMed consent form and a Nemours consent form for "transcatheter occlusion: fenestrations (covered stent, amplatzer)." At the same time as the CP stent implantation, Patient #10 received a pacemaker. Subsequently, one of the pacemaker leads dislodged and was re-positioned. Otherwise, the CP stent implantation corrected Patient #10's right atrial baffle leak. The Nemours Cardiac Center evaluated Patient #10 on January 31, 2003, at which time Patient #10 was asymptomatic of cardiac distress.

Patient # 11

On January 27, 2003, Dr. Murphy performed transcatheter completion of the Fontan procedure in Patient #11 with a CP stent. Patient #11's father signed a Nemours consent form for "Fontan completion by covered stent placement." The father's signature was not dated. The Hospital has no record that Patient #11's parents signed the NuMed consent form at the time of Patient #11's procedure. In October 2003, Dr. Murdison and cardiac staff members submitted to NuMed and the FDA a NuMed informed consent document signed by Patient #11's father, Dore Klenk (Cardiac Center technician) and Dr. Murphy. Although signed and dated in October 2003, the document reflects a date of "1/27/03," the date of Patient #11's procedure. **Tab 26.** This issue is discussed more fully below. Patient #11's procedure went well, aside from a short-lived pleural effusion after the implantation of the CP stent. Patient #11 was discharged from the Nemours Cardiac Center shortly before February 6, 2003. As of July 23, 2003, Patient #11 was doing well.

Patient #12

On March 4, 2003, Dr. Murphy performed transcatheter completion of the Fontan procedure in Patient #12 with two CP stents. Dr. Murphy implanted both stents during the same procedure. Patient #12's parent or guardian executed a Nemours consent form for "transcatheter placement of intravascular stent: Fontan completion" and a NuMed consent form on the day of Patient #12's procedure. Aside from bilateral pleural effusions and a residual right-to-left shunt, Patient #12 tolerated well the completion of the Fontan procedure with a CP stent. Patient #12 was discharged from the Nemours Cardiac Center on March 11, 2003. As of March 25, 2003, Patient #12 was stable and appeared well.

Patient #13

On April 7, 2003, Dr. Murphy attempted transcatheter completion of the Fontan procedure in Patient #13 with two CP stents. Patient #13's parent executed a Nemours consent form and a NuMed consent form on April 7, 2003. Dr. Murphy implanted the first CP stent in Patient #13 on April 7, 2003, and implanted the second on the same day to correct a right-to-left shunt involving the first CP stent. Following this first procedure, Patient #13 developed hypoxia and was returned to the catheterization lab on April 8, 2003 for insertion of a third CP stent to complete the cavopulmonary connection. The third CP stent failed to correct Patient #13's persistent hypoxia, and on April 8, 2003, Dr. Norwood surgically removed the CP stents from

Patient #13 and completed the Fontan procedure surgically. In the weeks after the procedure, Patient #13 exhibited multiple organ dysfunction and failure. She was never discharged from the Hospital and died on May 6, 2003, of multiple organ failure.

Patient #14

On April 8, 2003, Dr. Murphy performed transcatheter completion of the Fontan procedure in Patient #14 with the CP stent. Patient #14's parent executed the Nemours consent form for "[t]ranscatheter placement of intravascular stent: Fontan [c]ompletion" and the NuMed consent form on April 8, 2003. On the morning of April 9, 2003, Patient #14 became severely cyanotic. The Nemours Cardiac Center staff returned Patient #14 to the cardiac catheterization lab and Dr. Murphy implanted a second stent in Patient #14 on April 9, 2003, to correct a right-to-left shunt of the first stent. After the second procedure, Patient #14 developed right pleural fluid collections that required intermittent aspirations through a right pleural catheter. At the time of Patient #14's discharge on April 17, 2003, Patient #14 was alert, interactive and free of pleural effusions. Patient #14 was also doing well at a June 24, 2003 evaluation with the Nemours Cardiac Center.

Patient #15

On May 1, 2003, Patient #15 underwent transcatheter completion of the Fontan procedure with the CP stent. Patient #15's father executed the NuMed consent form and the Nemours consent form for "[t]ranscatheter placement of intravascular stent: Fontan Completion" on April 28, 2003. Dr. Murphy performed the CP stent implantations. On May 1, 2003, Dr. Murphy deployed one CP stent in Patient #15, and then a second stent to remedy a residual right-to-left shunt. On May 19, 2003, Dr. Gidding reported a leak in the center of the stent. Patient #15 had persistent cyanosis and a July 15, 2003 follow-up evaluation at the Nemours Cardiac Center detected a right-to-left shunt at the center of the CP stent. As is detailed below, Patient #15 underwent implantation of a third CP stent on July 18, 2003.

Patient #16

On May 5, 2003, Dr. Murphy implanted two CP stents in Patient #16 to create a total cavopulmonary connection and complete the Fontan procedure. Patient #16's father executed the NuMed consent form and a Nemours consent form for "[t]ranscatheter placement of intravascular stent: for Fontan completion" on the day of Patient #16's procedure. After the procedure, Patient #16 developed a left pleural effusion, which was corrected with a pleural catheter. Patient #16 was discharged from the Nemours Cardiac Center on May 12, 2003. Patient #16 was doing well at a visit with the Nemours Cardiac Center on September 2, 2003.

F. CP Stent Recall and NuMed Requests for Information

On May 14, 2003, NuMed notified Dr. Murphy that it had notified the FDA "of the unapproved usage of the CP stent for cases in the U.S." **Tab 27.** NuMed stated that Dr.

Murphy had received stents "between January 2000 and May 2003,"[13] and asked that he send NuMed (1) patient initials or ID numbers, (2) consent forms, (3) catheterization summaries and (4) follow-up information for each patient who received the CP stent. Dr. Murphy and the Nemours Cardiac Center did not immediately respond to this request. As of May 14, 2003, Dr. Murphy had not provided information to NuMed about his prior use of the CP stent.

Dr. Murphy learned of the CP stent recall no later than June 26, 2003 when he received a letter from NuMed headed "URGENT MEDICAL DEVICE RECALL."[14] The letter asked that Dr. Murphy account for the CP stents that he had ordered from NuMed, and advised Dr. Murphy that the CP stent was not to be used except in emergency use or on a compassionate use basis. **Tab 22.** The June 26, 2003 letter requested that for each CP stent recipient, Dr. Murphy send to NuMed (1) consent forms, (2) patient summaries, (3) reports on complications and adverse events, (4) notification of device malfunctions, and (5) follow-up data. Dr. Murphy and the Nemours Cardiac Center did not immediately respond to this request.

On August 8, 2003, Dr. Murphy submitted to NuMed a letter requesting NuMed's assistance in submitting 20 compassionate use requests to the FDA. **Tab 28.** This letter was accompanied by a narrative from Dr. Norwood regarding the history of the Fontan procedure, hypoplastic left heart syndrome and the use of the CP stent. Dr. Norwood stated that the results of Fontan completions with the CP stent "have been astounding . . . there has been no mortality" and that "completion of a Fontan type procedure with a covered stent in the catheterization laboratory is a pertinent example" of recent "remarkable developments" in cardiac care. NuMed responded on August 22, 2003 and informed Dr. Murphy that the FDA had rejected all but four of the compassionate use requests. The FDA requested the following additional information on those four prospective compassionate use patients: (1) a description of each patient's condition and the circumstances necessitating treatment; (2) a discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition; (3) an identification of any deviations in the approved clinical protocol that may be needed in order to treat each patient;[15] and (4) the patient protection measures that will be followed. Dr. Murphy responded with a description of the condition of the four patients on August 27, 2003. **Tab 29.**

On September 10, 2003, in response to a Dr. Murphy inquiry, Ms. LaFlesh (NuMed) informed Dr. Murphy in writing that the FDA would not approve the pending compassionate use requests. She stated that to expedite the approval process, Dr. Murphy should send her all information on the Fontan completions that he had already performed with the CP stent, plus the patient follow-up information and informed consent forms that NuMed previously requested. Dr. Murphy and the Nemours Cardiac Center did not immediately respond to this request.

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[13] NuMed's records show that Dr. Murphy had actually received CP stents between January 2002 and May 2003.

[14] Dr. Murphy did not advise the IRB or other Hospital officials about the recall.

[15] The Hospital is not aware of an "approved clinical protocol" for the CP stent.

On September 25, 2003, the FDA called NuMed and Dr. Murphy to gain more information about pending compassionate use requests. According to an FDA letter, Dr. Murphy informed the FDA of thirteen prior transcatheter completions of the Fontan procedure with the CP stent.[16] The FDA stated that it learned for the first time in this telephone call that Dr. Murphy had previously implanted the CP stent in patients. **Tab 30.**

NuMed and the FDA continued to request information from Dr. Murphy regarding both past and prospective uses of the CP stent. Both NuMed and the FDA repeatedly advised Dr. Murphy that the stent would not be approved for compassionate use or a clinical study until the requested information was received and reviewed. On September 29, 2003, NuMed forwarded to Dr. Murphy an email from Donna Buckley of the FDA, which requested follow-up information regarding three compassionate use cases. **Tab 31.** On September 30, 2003, Douglas Villnave of NuMed informed Dr. Murphy that the FDA had requested (1) the most recent follow-up information on all patients who received the CP stent, (2) consent forms for each patient, and (3) an accounting of all stents that the Nemours Cardiac Center received from NuMed. **Tab 32.** Mr. Villnave further requested a written explanation if any of the above information was not available.

Finally, on October 2, 2003, the FDA faxed a letter to NuMed, which requested a clinical summary of the thirteen Fontan cases that Dr. Murphy mentioned in the September 25, 2003 call and for each potential compassionate use patient (1) a description of the patient's condition, (2) a discussion of why alternative therapies were unsatisfactory, and (3) confirmation that Dr. Murphy will follow appropriate patient protection measures. **Tab 30.** NuMed immediately provided a copy of the letter to Dr. Murphy. This letter was also not provided to the IRB or the Hospital.

G. Nemours Cardiac Center Response to Multiple Requests by NuMed and FDA

Between September 25, 2003, and October 2, 2003, Dr. Murphy and the Nemours Cardiac Center staff began gathering materials to respond to the multiple requests from NuMed and the FDA. Dr. Murphy stated that he asked Dr. Murdison to supervise the response to NuMed. On October 6, 2003, a package of requested material was sent by Federal Express to NuMed.[17] This material included informed consent forms, catheterization reports and other relevant medical records, and follow-up reports which included all relevant complications. As described more fully below, this material also included two informed consent forms prepared and signed on or about October 2, 2003, which purported to be original informed consent forms signed much earlier on the actual date of the stent placement procedure. In late October 2003, Dr. Murphy provided NuMed with the requested information related to three compassionate use

[16] By September 25, 2003, Dr. Murphy had implanted the CP stent in 16 patients. One patient was not a Fontan patient. A second patient received three CP stents, which were removed almost immediately. The Fontan procedure was completed surgically for that patient, rather than by the transcatheter method. This patient died in May 2003.

[17] Despite FDA's understanding that Dr. Murphy had used the CP stent in 13 Fontan completions, Dr. Murphy provided the requested information for all 17 patients, including one patient who had the stent implanted on an emergency use basis on October 2, 2003.

requests. On November 5, 2003, Dr. Murphy sent a clinical summary report to NuMed regarding all prior uses of the CP stent in Fontan completion.

1. Missing Consent Forms

On October 2, 2003, Dr. Murphy, Dr. Murdison and other staff members determined that three NuMed informed consent documents were missing for Patients #4, 7 and 11. Dr. Murphy and Dr. Murdison both stated that they decided to contact the three affected families and ask them to sign replacement informed consent forms.[18] Dr. Murphy and Dr. Murdison both stated that they decided to advise the parents to sign and date the informed consent forms and indicate the "date of procedure" on the form as well. Both Dr. Murphy and Dr. Murdison stated that they did not intend to "backdate" the documents, but rather, they intended to ensure that the signed documents merely reflected what they were certain had properly occurred. Dr. Murdison agreed to contact the families. Both Dr. Murphy and Dr. Murdison stated that Dr. Norwood and Nemours Cardiac Center Executive Administrator John Walsh were aware of the missing informed consent documents and understood that the parents would be asked to sign replacement forms.

The Nemours Cardiac Center staff could not locate NuMed consent forms for patients #4, #7 and #11. Dr. Murdison stated that he called the three families, but could not remember whether he instructed them on how to sign and date the replacement NuMed consent forms.[19] After calling the families, Dr. Murdison stated that he faxed NuMed consent forms to #11's parents, #4's grandmother and #7's father. Dr. Murphy apparently pre-signed each of the consent forms before Dr. Murdison faxed them to the families. Dr. Murphy did not date his signature.

Mr. and Mrs. #7 received Dr. Murdison's fax on October 2, 2003. The cover sheet read: "Please review attached consent from NuMed, Inc., initial page 1 and sign page 2 and send back. Her date of procedure was 10/14/2002. Thanks for your help." **Tab 33.** Mr. and Mrs. #7 refused to sign the NuMed informed consent form. As a result, Dr. Murdison prepared a memorandum, which advised that Patient #7's informed consent forms were not available. **Tab 25.**

Dr. Murdison spoke to Patient #4's grandmother and requested the replacement form. Patient #4's father signed the NuMed consent form on October 2, 2003, but dated his signature "7/08/02," which was the date Patient #4 was implanted with the CP stent. Upon receipt of this document, Dr. Murdison knew that the document had not been executed on July 8, 2002, but directed Dore Klenk to sign the form as a witness and to write "7/08/02" next to her

[18] Approximately one month later, in mid-November, after a parent complaint, Dr. Roy Proujansky, Chief Executive of the Practice for the Hospital, asked Dr. Murphy about FDA requests for information. As reflected in the FDA Establishment Inspection Report (p. 12), Dr. Murphy stated that he was unable to locate one informed consent document for the parents who filed a complaint.

[19] Dore Klenk, a Cardiac Center technician, said that she was present when Dr. Murdison called each of the patient families, and that she recalled that Dr. Murdison told each of the families how to sign and date the NuMed consent forms to reflect both the date of signature and the date of procedure.

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signature. This informed consent document was provided to NuMed by Carol Muscar, a research coordinator assigned to the Nemours Cardiac Center, on October 6, 2003. **Tab 24.** Ms. Muscar knew that three original forms were missing and that two signed replacement forms were provided.

Similarly, Dr. Murdison called patient #11's parents and asked them to sign a replacement NuMed consent form. Patient #11's father signed the NuMed consent form on or about October 2, 2003, but dated his signature "1/27/03," which was the date Patient #11 was implanted with the CP stent. Dr. Murdison knew that the form had not been executed on January 27, 2003, but directed Dore Klenk to sign the form as a witness and to write "1/27/03" next to her signature. This replacement informed consent document was also provided to NuMed by Carol Muscar. **Tab 26.**

2. Claimed Discovery of Missing Consent Forms

On February 23, 2004, during the course of our investigation, Dr. Murdison stated that he again searched the Cardiac Center for the missing consent forms. He stated that he found the missing consent forms together in a desk drawer among other unrelated documents. Dr. Murdison provided four NuMed informed consent forms for the three patients as described below.

A NuMed informed consent form was produced by Dr. Murdison for Patient #7.[20] **Tab 34.** The document appeared to be signed and dated by Patient #7's father, witnessed by Chris Panchelli (a Nemours Cardiac Center nurse) and Dr. John Murphy. All signatures were dated "10/14/02," which was the date Patient #7 received the CP stent.

A NuMed informed consent document was produced by Dr. Murdison for Patient #11. **Tab 35.** The document appeared to be signed by Patient #11's father but not dated. The document did not have any other signature by a witness or physician. Finally, two NuMed informed consent documents were produced by Dr. Murdison with the printed name of Patient #4 on the front page. **Tab 36.** These two forms have no signatures from a parent, witness or physician.

Upon receipt of these documents, the Hospital took two immediate steps. The Hospital first provided these documents to state regulators who had previously inquired about the missing forms. Second, the Hospital engaged the services of an expert document examiner. On March 24, 2004, the document examiner provided a preliminary report regarding the authenticity of one signature, which caused the Hospital to take further action as discussed with the FDA. The matter is still under investigation.

[20] The two-page document was not produced intact. Two unrelated NuMed documents were located between pages one and two of the NuMed informed consent document.

3. Disclosure of Adverse Events and Complications Information

On October 6, 2003, the information provided to NuMed included catheterization reports and follow-up reports reflecting the patients' conditions at various milestones. This information included the report that Patient #13 died on May 6, 2003, after three stents were implanted and then removed on April 8, 2003, and after surgical completion of the Fontan. Other patient complications were also reported in the October 6, 2003 submission to NuMed. In addition, Dr. Murphy provided two clinical summaries to NuMed on November 5, 2003, which also report patient complications.

The IRB did not receive any notice of adverse events or patient complications for CP stent patients until receiving a report on December 15, 2003 regarding the dislodgment of a stent implanted in Patient #19 in December 2003, which is addressed below. The FDA and NuMed received all requested information regarding patient outcomes in October 2003.

H. IRB Knowledge of the Use of the Stent

Dr. Murphy did not properly notify the IRB about his use of the CP stent.[21] Dr. Murphy relied on informal and incomplete conversations with an individual IRB member and failed to provide adequate information to permit the IRB to exercise its oversight authority. Dr. Murphy's reliance on an informal conversation was unreasonable and contrary to Hospital policy. All submissions to the IRB must be in writing and must provide sufficient information to allow the IRB to make a determination. As reflected below, the Hospital intends to implement significant corrective action to ensure this activity never occurs again.

Dr. Murphy stated that he first discussed the use of the stent with Dr. Rob Locke, the Vice-Chair of the IRB, in early Spring 2002. However, it appears from the Hospital's investigation that Dr. Locke believed that Dr. Murphy was discussing possible future use of an approved device for Fontan completions. Dr. Locke stated that he did not raise Dr. Murphy's planned use of the CP stent with the IRB, because he considered the non-research use of an approved device in the course of clinical care to be beyond the jurisdiction of the IRB.

On July 11, 2003, the IRB first learned that Dr. Murphy and the physicians in the Nemours Cardiac Center planned to implant the CP stent in a patient. Dr. Murphy sent a letter to Dr. Locke, stating that the Nemours Cardiac Center was "seeking the approval of the United States Food and Drug Administration on a compassionate use basis to employ the NuMed covered stent for the completion of a Fontan procedure in the catheterization laboratory and the treatment of aortic coarctation in older patients." **Tab 37**. Dr. Murphy stated in the letter that "[w]hile I know that this institution does not require IRB approval for such a clinical use, I am seeking your endorsement for our application to the FDA." Dr. Murphy did not advise the IRB that he had already implanted 23 stents in 15 patients in the previous 15 months, nor that the

[21] Dr. Murphy also did not notify hospital officials about his use of the stent. On page 12 of the Establishment Inspection Report, the statement that Dr. Proujansky "had known of the use of the NuMed stent in the hospital" is incorrect. Dr. Proujansky knew that Dr. Murphy was using a stent to complete the Fontan procedure, but did not know that the stent was a "NuMed stent" or that it was an unapproved device.

device was recalled in the previous month. Dr. Locke responded on behalf of the IRB. **Tab 38.** Neither the Hospital nor the IRB received any further reports or information from Dr. Murphy or NuMed regarding use of the CP stent or patient-specific compassionate use requests for use of the CP stent. As described more fully below, on July 18, 2003, Patient #15 received a CP stent without notice to or approval from the IRB or FDA.

Beginning in October 2003, the IRB first learned of the actual use of the CP stent through a patient complaint. The IRB first received information about the actual use of the CP stent on October 14, 2003, when Janet Leary-Prowse (an IRB Administrative Assistant) spoke with Patient #7's parent. The parent informed Ms. Leary-Prowse that Dr. Murphy implanted a "NuMed Palmaz" stent in Patient #7 during cardiac surgery to complete the Fontan procedure. Ms. Leary-Prowse reviewed the IRB's files for information regarding the Palmaz stent, NuMed stents and studies by Dr. Murphy using either the Palmaz stent or NuMed stents. She found none.

The IRB next received information regarding use of the CP stent on October 22, 2003, when the same parent again inquired of Ms. Leary-Prowse about IRB oversight of the Nemours Cardiac Center's use of the "NuMed stent." Ms. Leary-Prowse passed the details of her conversation with the parent to the IRB chair and Barbara Weinman Supplee, a member of the Hospital's Risk Management department. On October 22, 2003, Ms. Leary-Prowse learned for the first time, through a search on the Internet, that the CP stent was subject to a recall on June 26, 2003. On October 27, 2003, Ms. Weinman Supplee met with John Walsh. During that meeting, John Walsh told Ms. Weinman Supplee that the stent was "available by prescription" and that the FDA was "not involved" with the use of the stent before the June 26, 2003 recall. The IRB chair received a report on Ms. Weinman Supplee's discussion with John Walsh.

The IRB learned that the CP stent was an unapproved device on November 26, 2003, when Dr. Vicky Funanage (Director of Biomedical Research) saw the NuMed consent form for the first time and advised the IRB Chair. At this point, however, the IRB still did not know how long the CP stent had been in use by the Nemours Cardiac Center or the number of patients who received CP stents. The IRB then began its preliminary investigation of the CP stent.[22] On December 8, 2003, Commander Joseph Despins informed Hospital and IRB representatives that Dr. Murphy and the Nemours Cardiac Center physicians had been using the stent since April 2002. On December 9, 2003, during a meeting with Dr. Norwood and Dr. Murphy, the IRB learned for the first time that Dr. Murphy and other physicians had implanted 32 stents in at least 17 patients between April 2002 and December 9, 2003.[23]

[22] Hospital officials investigated as well. Dr. Proujansky met with Dr. Murphy in mid-November. He recalls Dr. Murphy stating that the CP stent was used in adults for certain indications. Contrary to the Establishment Inspection Report (p. 14), Dr. Proujansky does not recall Dr. Murphy stating that the CP stent was approved for adult use, rather, Dr. Proujansky assumed that he was talking about an approved device.

[23] The Hospital has since determined that by December 9, 2003, physicians at the Nemours Cardiac Center had used the CP stent in 20 patients, one of whom received the CP stent on an emergency use basis and three of whom received the stent on an FDA-approved compassionate use basis.

EXHIBIT K

I. Second Stent Implantation in Patient #15

As noted above, Patient #15 underwent transcatheter completion of the Fontan procedure on May 1, 2003. Patient #15 was re-admitted to the Nemours Cardiac Center on July 15, 2003. Patient #15 was severely cyanotic upon admission. Patient #15's mother executed a Nemours consent form for "Transcatheter placement of intravascular stent: IVC-RA junction" on July 17, 2003. The parents did not execute a new NuMed consent form. Patient #15 underwent an exploratory catheterization, which showed that the CP stent Patient #15 had received on May 1, 2003, was not properly seated. On July 18, 2003, Dr. Murphy implanted a CP stent in Patient #15. Based on the Hospital's investigation, Patient #15's clinical condition was considered an emergency by Dr. Murphy. Dr. Murphy and the Nemours Cardiac Center staff did not notify the IRB or file any required after-action reports or other post-emergency use reports with the IRB or the FDA. Despite notice from the FDA that the CP stent could be used only in accordance with emergency use or compassionate use procedures, Dr. Murphy did not follow either procedure, or advise the IRB.

J. Emergency and Compassionate Use of the CP Stent

As stated above, on or about August 8, 2003, Dr. Murphy submitted to NuMed a list of 20 patients for whom he was seeking compassionate use approval from the FDA. On August 18, 2003, the FDA rejected all but four of the compassionate use requests and said that it would consider the remaining four requests upon receipt of further information. **Tab 39.** The remaining compassionate use requests were for patients #17, #18, #19, and #20, whose scheduled transcatheter Fontan procedures were canceled after the June 26, 2003 recall.

~~During his September 25, 2003 call with FDA representatives, Dr. Murphy and~~ the FDA agreed that one patient, Patient #17, was in a clinical situation that warranted emergency use of the CP stent. The remaining three patients were still considered prospective compassionate use patients. These four post-recall cases are described below

Emergency Use

Patient #17

On October 2, 2003, Dr. Murphy implanted a CP stent in Patient #17 on an emergency use basis with FDA approval. He did not notify the IRB prior to this procedure. Patient #17's parents executed a Nemours consent form for "[c]ompletion of Fontan using NuMed covered stent" and a NuMed consent form. After the procedure, Patient #17 developed pleural and peritoneal effusions and remained on ventilation for four days. Patient #17 was removed from ventilation on the fifth day. On October 7 and 8, 2003, Dr. Murphy sent NuMed an after-action report of the emergency use of the CP stent for the procedure on Patient #17, along with other materials required by NuMed and the FDA. Dr. Murphy also sent a copy of Dr. Locke's July 16, 2003 letter.[24] The Nemours Cardiac Center discharged Patient #17 in good

[24] Dr. Locke's July 16, 2003 letter was not a satisfactory substitute for the required notice to the IRB Chair regarding the use of investigational devices in an emergency or compassionate use situation.

health on October 27, 2003. The IRB was not notified about the emergency use of the stent, which constituted a violation of Hospital policy.

Compassionate Use

On October 27, 2003, Dr. Murphy sent NuMed an application for compassionate use of the CP stent in Patient #18. **Tab 40.** On October 30, 2003, Dr. Murphy sent NuMed similar applications for patients #19 and #20.[25] **Tab 41.** Ms. LaFlesh forwarded those applications to the FDA on October 30, 2003. In violation of Hospital policy, Dr. Murphy did not send these compassionate use applications to the IRB.

On November 10, 2003, NuMed received notice from the FDA that the FDA approved Dr. Murphy's compassionate use requests for patients #18, #19, and #20. **Tab 42.** As detailed below, Dr. Murphy implanted CP stents in each of these patients, but did not provide notice to the IRB.

Patient #18

On November 21, 2003, Dr. Murphy used two CP stents for transcatheter completion of the Fontan procedure in Patient #18. The patient's parents executed a Nemours consent form for "[c]ompletion of Fontan using NuMed covered stent" and a revised NuMed consent form for the procedure.[26] Patient #18 was discharged from the Nemours Cardiac Center on November 24, 2003.

Patient #19

On December 2, 2003, Dr. Murdison and Dr. Murphy implanted a CP stent in Patient #19 for transcatheter completion of the Fontan procedure. The patient's parents executed a Nemours consent form for "[c]ompletion of Fontan using NuMed covered stent" and a revised NuMed consent form. After the procedure, Patient #19 became acutely cyanotic because the NuMed CP stent became dislodged after its insertion. In a second procedure, Dr. Murphy inserted a second CP stent in Patient #19. The patient's condition improved. Dr. Murphy submitted an adverse event report to the IRB, reporting the dislodgment. **Tab 43.**

Patient #20

Finally, on December 4, 2003, Dr. Murdison and Dr. Murphy implanted a CP stent in Patient #20 for transcatheter completion of the Fontan procedure. The patient's parents executed both a Nemours consent form for "[c]ompletion of Fontan using NuMed covered stent"

[25] The three compassionate use applications include the same July 16, 2003 letter from Dr. Locke.

[26] Prior to this procedure, NuMed and the FDA revised the NuMed consent form for the purpose of the "compassionate use" cases. The phrase "investigational stage" was substituted with "compassionate use." There were several other significant changes made to the informed consent document. The IRB was not aware of the specific compassionate use cases and was not provided an opportunity to review or approve the informed consent document, as required by Hospital policy.

and a revised NuMed consent form. The procedure went well, although Patient #20 developed small right and left pleural effusions. Patient #20 was discharged on January 13, 2004.

K. Patient Complaint by the Patient #7 Family

The Hospital and the IRB received several complaints from the Patient #7 family regarding patient care and the CP stent. As reflected below, the complaints were not well-handled. Both the Hospital and the IRB intend to implement significant corrective action regarding patient complaint procedures.

On March 27, 2003, Mr. and Mrs. #7 worked with the Hospital's Patient Relations Department to submit a complaint that the Nemours Cardiac Center failed to provide adequate care to their child, Patient #7, by failing to timely evaluate whether the patient needed a bronchoscopy for the treatment of plastic bronchitis. They amended their complaint on April 7, 2003, to state that because of the Nemours Cardiac Center's lack of proper care, Patient #7 had had to be resuscitated during her transfer to the pediatric intensive care unit, and then had to undergo an emergency bronchoscopy. We agree with Commander Despins' report that the Patient #7 family complaint (filed in March 2003) was referred to the Cardiac Center and others within the Hospital, none of whom handled the complaint properly.

Mrs. #7 properly complained when she received a telephone call on October 2, 2003, from Dr. Kenneth Murdison asking her to sign and date an informed consent form for a procedure performed one year earlier. Mrs. #7 complained to both Hospital and IRB officials about this matter, as correctly outlined in Commander Despins' report. On October 30, 2003, Thomas Ferry (Hospital Administrator) wrote a letter to the parents, memorializing a conversation between Mrs. #7 and Mr. Ferry during the week of October 20, 2003. Mr. Ferry assured them that the Hospital would follow up on their complaints and would be in touch with them. The Hospital did follow up, which included this investigation.

On January 20, 2004, Mrs. #7 requested a copy of the letter of complaint she filed in March 2003 with Patient Relations. On January 28, 2004, Dr. Proujansky attempted to call Mrs. #7 to clarify her request, but he was only able to leave a voicemail. Dr. Proujansky then spoke with Mr. #7. Dr. Proujansky asked him for background on the nature of the complaint, and asked what document they were seeking. Mr. #7 informed Dr. Proujansky that they wanted a copy of the March 27, 2003 complaint and the addendum thereto, which Dr. Proujansky agreed to provide. Dr. Proujansky reiterated that the Hospital was in the midst of an investigation of their complaint and other matters. Dr. Proujansky again promised to meet with the family. The Hospital has requested a date from the parents of Patient #7 to meet with Dr. Proujansky for an explanation of the CP stent and their daughter's medical care.

The Hospital and IRB will implement significant corrective action to ensure that patient complaints are properly handled in the future.

L. Informed Consent

Informed consent requirements vary based on the distinction between research and the practice of medicine. Delaware physicians engaged in the practice of medicine are required to provide information about a treatment or procedure to the extent customarily given to

patients by health care providers in the same field of medicine. Likewise, informed consent is one of the fundamental principles of ethical research with human subjects. A research protocol will require an approved informed consent document containing the elements in 45 CFR § 46.116. The IRB reviews informed consent documents and may also supplement informed consent procedures.

Here, Dr. Murphy and other physicians were not using the CP stent as part of a research protocol. If they were engaged in such a protocol, the NuMed informed consent document would certainly have been reviewed and modified by this IRB. In the absence of a research context, however, Dr. Murphy, while obtaining informed consent to any particular patient, was under no obligation to use the manufacturer's documents.

Nonetheless, Dr. Murphy and other physicians used the NuMed informed consent form for nearly every patient. The form classifies the CP stent as an investigational device. To the extent that the NuMed consent form gives an impression that the device is part of a supervised study or investigation, it is misleading.

The Hospital and IRB will implement significant corrective action, described more fully below, to ensure that all informed consent documents, subject to IRB jurisdiction, are reviewed and approved by the IRB before use.

M. Medical Device Reporting

Medical device reporting requirements also vary based on the distinction between research use of the device and use of the device in the practice of medicine. Medical Device Reporting Regulations require a "user facility" to report to the FDA and to the manufacturer "as soon as practicable, but not later than 10 work days after becoming aware of the information" deaths that may have been caused or contributed to by a device. 21 C.F.R. § 803.30. The regulations also require user facilities to report serious injuries that may have been caused or contributed to by a device to the manufacturer, or if the manufacturer is not known, to the FDA "as soon as practicable, but not later than 10 work days after becoming aware of the information." The Hospital has a medical device reporting policy that parallels these regulations.

In the research context, adverse events must be reported under various rules depending on the nature and severity of the event, as well as the relationship between the device and the event. Research protocols routinely require an initial report to the IRB. Here, there were no reports to the IRB of adverse events regarding the CP stent, until one occasion after the device recall, in December 2003.

Dr. Murphy was not conducting research in the context of any established clinical study protocol. Therefore, only the medical device reporting regulations applied. Here, the medical device reporting requirements would have triggered a reporting obligation in the case of one patient who died of multiple organ failure one month after three CP stents were implanted and then removed and the Fontan procedure was completed surgically.

The Hospital and IRB will implement significant corrective action, described more fully below, to ensure that medical device reporting obligations are satisfied regardless of whether the event occurred in a research context.

N. Cooperation with FDA and Third-Party Audit

On December 1, 2003, Commander Despins of the FDA commenced his audit of the Hospital IRB and of the use of the CP stent at the Hospital. The Hospital provided Commander Despins with copies of all requested materials and produced for interview all requested Hospital staff. Commander Despins concluded his audit of the Hospital IRB on December 4, 2003, and conducted the exit conference on December 8, 2003. At the exit conference, Commander Despins complimented the IRB, cited no deficiencies, and charged the IRB with further investigation of Dr. Murphy's use of the CP stent. This report is the result of the IRB's comprehensive investigation.

On December 17, 2003, Brian Ostrander of MedTrials, Inc. conducted and concluded a third-party audit of the Nemours Cardiac Center's records on the CP stent. The MedTrials auditor completed his audit and apparently found no discrepancies between the files that the Nemours Cardiac Center had submitted to NuMed and the ten files to which he had access.

II. CORRECTIVE ACTION PLAN

The Hospital acknowledges the problems identified above and commits to the comprehensive corrective measures necessary to ensure patient care, patient protection and patient relations remain central to the Hospital's mission. This corrective action plan will change the organizational structure as well as implement and clarify procedures for Hospital physicians and staff to ensure effective oversight of both patient care and clinical research. Specifically, the Hospital will:

- Change the leadership and structure of the Nemours Cardiac Center.
- Discipline Dr. Murphy and others for violation of Hospital policies and standards.
- Create a Human Subject Protection Department.
- Strengthen the acquisition process and the Products Committee.
- Conduct extensive training for the IRB, Hospital leadership, physicians, and hospital staff.
- Strengthen IRB policies and procedures.
- Establish a CP stent protocol to provide continuing care for all existing stent patients in the form of a prospective registry.
- Communicate with all CP stent patient families about the use of the stent and continuing care.
- Ensure the IRB has at least one member with medical device experience.

EXHIBIT K

- Ensure proper internal communications regarding innovative clinical care, research, and adverse events.
- Enhance the Hospital's Audit and Compliance Program, including specific support for the IRB and the Human Subject Protection Department.
- Meet with the Patient #7 family.
- Strengthen and improve patient relations procedures, including establishment of an ombudsperson position.
- Strengthen and streamline the Medical Device Reporting Program.

A. Organizational Structure

1. Nemours Cardiac Center Leadership Change

The Nemours Cardiac Center will no longer operate as an autonomous unit under the direction of Drs. Norwood and Murphy. The Hospital has already begun a programmatic and administrative overhaul, which included a change in leadership. Dr. Norwood and Dr. Murphy are no longer employees of the Hospital and are not providing professional or administrative services. The Cardiac Center now reports directly to Dr. Roy Proujansky, Chief Executive of the Practice. The Cardiac Center will conform its professional practice to all policies and procedures of the Hospital under appropriate oversight.

2. Discipline

Based in part on the issues discussed in this Report, the Hospital terminated its professional relationship with Dr. Murphy. Dr. Murdison was disciplined and additional discipline is under consideration as of the date of this report. The Hospital also suspended Dore Klenk for a day without pay and placed her on disciplinary probation. In addition, the Hospital placed Carol Muscar on disciplinary probation.

3. Human Subject Protection Department

The Hospital will form a new department for Human Subject Protection to provide education, counseling and audit support for Hospital physicians and staff. The new department will support the IRB, the Biomedical Research Department, the Chief Executive of the Practice and the Hospital leadership. The formation of this new department will include the hiring of at least 3 full-time employees, one of whom will hold departmental director-level authority at the Hospital. The Director of the Human Subject Protection Department will have a dotted-line reporting relationship to the IRB Chairman and a direct-line reporting relationship to the Vice President for Patient Operations.

The Hospital will commit resources to the Human Subject Protection Department to provide for an audit and compliance function. Teresa DuPree, Vice President for Quality, Audit and Corporate Compliance, will design and implement a plan to ensure compliance with policies and procedures regarding informed consent, medical devices, adverse event reporting as

well as patient relations matters. In addition, the Hospital will assign at least two auditors from the Compliance department to conduct audits on human subject protection matters such as informed consent and proper research methods at the Hospital on behalf of both the IRB and the Human Subject Protection Department. An audit workplan will be developed by the Vice President for Quality, Audit and Corporate Compliance, in coordination with the Human Subject Protection Department and the IRB, to assure compliance in all areas of human subject protection.

In August 2003, the IRB requested a voluntary self-assessment with the Office of Human Research Protections (OHRP). That visit is scheduled for April 27-28, 2004. The Hospital will request assistance from OHRP in the design and implementation of an effective Department of Human Subject Protections at the A.I. duPont Hospital for Children.

4. Products Committee

The Hospital will charge the existing Materials Management Department and the Products Committee with the responsibility for monitoring the acquisition and use of all devices in the Hospital. The Materials Management Department and the Products Committee have already begun an internal systems evaluation in anticipation of implementing this corrective action.

The Materials Management Department and the Products Committee will monitor the acquisition of all devices by physicians and staff in the Hospital. All devices and supplies purchased by the Hospital are purchased by Materials Management. The IRB will provide the Materials Management Department with a master list of all approved devices. If Materials Management receives an order for a new device or for a device from a new manufacturer, it will refer the device order to the Products Committee and notify the IRB. The Products Committee will then contact the manufacturer to determine the regulatory status and all approved uses of the device, as well as making its own determination of the regulatory status and approved uses of the device. After determining the regulatory status and approved uses of the device, the Products Committee will report its findings to the ordering physician, the physician's department head, the IRB and the Director, Human Subject Protection for determination of whether the new device is appropriate for patient care. The IRB will determine whether use of the device constitutes research.

5. Board of Managers Training

The Nemours Board of Managers will participate in a training program to emphasize the key elements of the Biomedical Research Program as well as the Human Subject Protection Program. This training will be planned by Dr. Vicky Funanage and Dr. Carlos Rosé, with the initial training program to be completed no later than June 2004. An annual refresher training program will be provided thereafter.

B. Institutional Review Board

1. IRB Retreat

The IRB held the third bi-annual retreat of the IRB leadership on March 11-12, 2004 to discuss some of the issues raised by its investigation into these matters and to devise plans for addressing specific problems and areas for improvement.

2. IRB Reporting Responsibilities

The IRB will report on its activities to the Board of Managers on a semi-annual basis.

3. CP Stent Protocol

The IRB will require a protocol from the Cardiac Center staff, in the form of a prospective registry, to provide for continuing review and appropriate patient care for all existing stent patients. Although the CP stents were implanted outside of an approved clinical study, these patients will receive continuing care under the oversight of the IRB.

The IRB will evaluate the existing medical records review protocol and permit the records review of existing stent patients for patient care only. The IRB will prohibit the use of the medical review protocol to support publications or presentations involving the past use of the CP stent.

The IRB has already directed the submission of a protocol and designated Dr. Samuel Gidding as the principal investigator for this matter. Dr. Gidding will also initiate a separate protocol for prospective emergency use of the CP stent.

4. Patient Communications

All stent patients' parents have been notified that their child was implanted with an unapproved device. Attending cardiologists personally telephoned each family to ensure continuity of patient care. Families of stent patients were advised to contact the Cardiac Center, now under the leadership of Drs. Rodrigo Neghme and Christian Pizzaro and under the supervision of Dr. Proujansky, if they have any questions or problems. Clinical follow-up continues for all CP stent patients and, where the parents so desire, the cardiologists are engaged in an ongoing relationship and discussion with the parents about both the health of their child and the CP stent. In addition, the Hospital will notify all CP stent recipients by certified mail that they were implanted with an unapproved device; whom to contact in the event of an emergency; the opportunity to seek care elsewhere; and how to report adverse events or other complications. The notice will also advise each patient that the medical records may be reviewed by the FDA. This letter will be reviewed by the IRB before it is sent to stent patients.

5. Medical Device Experience

The IRB membership will now require at least one member with significant medical device experience. This member must have demonstrated knowledge and experience

with device regulations regarding the distribution and use of devices, as well as medical device reporting. The IRB membership currently includes a member with that experience.

6. Policies and Procedures Overhaul

The IRB will revise its Policies and Procedures Manual to expand the available guidance on investigational devices. The IRB is presently engaged in outreach to other regional IRBs regarding their policies and procedures regarding medical devices. Michael Primiani, Ph.D., and Mary Clancy, R.N., are responsible for spearheading this effort.

The IRB will also revise its Policies and Procedures Manual section on receiving, processing and recording complaints by parents, research participants and subordinate staff. Dr. Vicky Funanage, Audrey Maxwell-Riddle and Ms. Clancy are responsible for this effort. Furthermore, the IRB will require the distribution of a patients' rights pamphlet to all research participants at the time of informed consent form signature.

7. IRB Training

The IRB will undergo a comprehensive refresher training program, which will emphasize key elements of the Nemours Human Subjects Protection Program. Although the FDA audit results revealed no IRB deficiencies, there is room for improvement.

As part of the refresher training, the IRB will re-emphasize its formal policy to require written requests and written responses for all IRB action.

8. Hospital Training

The IRB will work closely with the Human Subject Protection Department to implement an aggressive training program for all Hospital employees in the areas of research, medical devices, human subject protection and informed consent. The IRB has already begun preparing a curriculum regarding practical knowledge and Hospital-specific human subject protections to be included with the annual compliance training in which all Hospital staff participate. Dr. Funanage, Ms. Riddle and Ed Jones are responsible for this initiative, which will be completed in time for inclusion in the next annual training program.

With respect to research in particular, the IRB will continue to require all investigators and any Hospital staff involved in the informed consent process to take the University of Miami CITI training course levels one and two, and to complete the CITI 3 course semiannually thereafter. The IRB will also investigate adding a Hospital-specific information module to the CITI training program.

9. Informed Consent

The Hospital and IRB will implement a new policy that prohibits the use of any "outside" informed consent documents. The IRB will have sole approval authority for any informed consent document used in research. The Director, Human Subject Protection Department will have sole authority to approve all non-research informed consent documents.

Only approved informed consent documents may be used in the Hospital, and each document must contain the date of IRB or Human Subject Protection approval.

The IRB is in the process of evaluating whether its training materials are sufficient to instruct Hospital staff on the elements of proper and effective informed consent. If the materials are not sufficient, the IRB will create new training materials for informed consent in the research context. Finally, the IRB is revising its informed consent template to reflect the distinction between parental consent and parental permission.

10. IRB and Ethics Committee

The IRB and the Ethics Committee will establish a program to communicate with each other regarding innovative clinical care issues. The IRB has the sole authority to determine whether a particular project constitutes research. To ensure proper IRB review, the Ethics Committee will refer matters, as appropriate, involving new devices, drugs or procedures to the IRB to make the determination of whether the matter constitutes research.

11. Adverse Event Reporting

The IRB will institute differential reporting procedures for the different types of studies that are typically conducted under its aegis: observational, non-interventional and interventional. It has already begun the effort to improve its definitions of these terms and create appropriate policies and procedures for instructing investigators on these different adverse event reporting structures. The IRB will also revise the IRB approval letters to reflect the IRB's improved definitions of these categories of research and to provide specific instructions about adverse event reporting procedures.

C. Compliance and Audit

1. Self-Audit

The Vice President for Quality, Audit and Corporate Compliance will establish an annual audit workplan to ensure effective audits of key compliance areas are conducted in the Hospital. In addition, the Quality Assurance and Patient Safety Department will continue to conduct audits to ensure all departments adhere to federal and state regulations. Results of all audits will be reported to the Vice President for Patient Operations and the Board of Managers for appropriate action.

2. Materials Management and Medical Device Audits

The Vice President for Quality, Audit and Corporate Compliance will develop and implement a plan to specifically audit the following hospital functions:

a. Materials Management.

As detailed above, the Materials Management Department will evaluate all requests for devices in the Hospital. Audits will determine whether the Product Committee reviews all maters involving a new device or a new vendor.

b. Medical Device Logs.

All departments will maintain medical device logs documenting the FDA number or date of IRB approval for the use of any medical device. Medical device logs will be subject to audit.

D. Patient Relations

1. Review of Patient Relations Policies and Procedures

The Hospital will review existing policies and procedures for patient complaints and develop realistic timelines for effective response.

2. Meeting with the Patient #7 Family

The parents of Patient #7 made several complaints, none of which was well-handled. Dr. Proujansky has invited the parents to meet with him so he can provide a full explanation on behalf of the Hospital.

3. Patient Complaint Tracking Procedure

One Hospital Manager, not Patient Relations, must have responsibility and accountability for the proper response to a patient complaint. Patient Relations will be responsible for centrally tracking all complaints lodged in the Hospital. The relevant manager will be responsible for communicating with the patient in a timely manner. The Hospital will establish a tickler system to track complaints and to ensure all response requirements are satisfied.

4. Patient Relations Training

All Hospital employees will be trained on the proper handling of patient complaints.

5. Ombudsperson

The Hospital will create an ombudsperson position. The ombudsperson will report directly to the CEO of the Hospital. The ombudsperson will answer patient inquiries and serve as a patient advocate and advisor in dealings with medical staff and Hospital departments. Members of the Patient Relations staff have already begun performing this role.

6. Additional Resources

The Hospital will provide patients with written materials regarding resources for addressing patient concerns, and on contact information for the Patient Relations department and the ombudsperson.

7. Physician/Manager Professional Incentives

Annual performance reviews, compensation and credentialing decisions will require an assessment of each physician's and manager's compliance with patient relations procedures. Physicians and managers will be held accountable when patient relations standards are not satisfied. In addition, the Patient Relations department will report compliance/noncompliance with patient relations policies to the Hospital management.

E. Risk Management/Medical Device Reporting

1. Streamline Reporting Requirements

The Hospital will create a single process for reporting all possible adverse events to Risk Management, which will involve an automated system for the electronic submission of adverse event reports to the risk managers. The Risk Management Director will then ensure proper follow-up and medical review of all internally reported events, and report events to the FDA and manufacturers as appropriate after thorough, timely review.

2. Education and Training

The Risk Management department will educate all medical and administrative staff about the thresholds for and timing of reporting adverse events to the Risk Management Department, the process of submitting those reports and the resources available to answer questions regarding event reporting.

3. Additional Resources

The Risk Management department will place guidance documents, policies and procedures (as well as information about available consulting and support) on the Nemours intranet.

III. FOIA CONFIDENTIAL TREATMENT REQUEST

We request that confidential treatment be accorded to (i) this letter and supporting documents and (ii) any transcripts, notes, memoranda or other records created by or at the direction of the Food and Drug Administration, the Office of Human Research Protections, their officers or staff members that reflect, refer or relate to this letter or any of the materials we have produced.

These documents are being provided to you solely in connection with the FDA investigation. Accordingly, please promptly inform Maryanne Donaghy, Esq., A.I. du Pont Hospital for Children, 1600 Rockland Road, P.O. Box 269, Wilmington, DE, 19899 of any request, including any request under the Freedom of Information Act, seeking access to any of the foregoing records, including this letter and any of the supporting materials we have produced, to enable us to substantiate the grounds for confidential treatment, unless the Department of Health and Human Services and FDA intends to deny such request for access on other grounds.

Sincerely,

David J. Bailey, MD, MBA
VP Patient Operations and Chief Operating Officer

Carlos Rosé, MD
Chair, Institutional Review Board
Chief, Division of Rheumatology

EXHIBIT K

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