MEDICAL DEVICE ASSISTANCE, INC.

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Expert Report of Suzanne Parisian, M.D.

Re: Pantopaque March 30, 2002

I. Qualifications

Since August 1995, I, Suzanne Parisian, M..D. have been President and founder of Medical Device Assistance, Inc., a regulatory and medical consulting firm specializing in matters involving the United States Food and Drug Administration's regulation of medical products. I received my Medical Degree (M.D) from the University of South Florida in 1978 and am Board Certified in Anatomic and Clinical Pathology. From 1991 to 1995, I served as a Commissioned Officer in the United States Public Health Service and achieved the rank of Commander. During this time period, I was primarily assigned to the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA). Concurrently, during l991 to l995, I was also assigned clinical responsibilities at the Armed Forces Institute of Pathology (AFIP), Office of the Medical Examiner for the Armed Forces, Washington, D.C.. From 1991 to 1993, I was a Medical Officer in the Office of Health Affairs (OHA) a staff office within the FDA. From March 1993 to December 1993, I was a Medical Officer in the Office of Device Evaluation, (ODE), Division of Reproductive Abdominal, Ear, Nose and Throat, and Radiology, (DRAERD) at the FDA. From January 1994 through June 1995, I was Chief Medical Officer for DRAERD at the FDA. My most current *curriculum vitae* is provided in Attachment "1" (http://www.mdassist.com).

ODE, FDA is the Office within CDRH responsible for the premarketing evaluation of product applications submitted by the manufacturer to market devices that are safe and effective within the United States. In ODE, I participated in the review of marketing applications as well as had the assigned responsibility of training new medical officers and scientific reviewers in application and labeling review at CDRH. I was an instructor in FDA's Staff College for the instruction of CDRH reviewers in the design and evaluation of clinical data contained within

premarketing applications.

While in OHA, I was a medical officer responsible for the review of mandatory adverse event reports submitted by a manufacturer, as well as the review of voluntary reports submitted by health care providers, patients and others. Within OHA, I was the primary clinician assigned responsibility to preside over 162 health risk assessments that were convened to advise FDA on the overall health risk of medical devices' performance issues, identification of public health safety issues, and to make recommendations to FDA regarding the subsequent regulatory actions that should be undertaken by FDA, health care providers, users groups and manufacturers in order to help protect the public's welfare. While in ODE, I performed an additional 100 health risk assessments and trained medical officers as to the procedure for conducting a health risk assessment.

At FDA, I participated with FDA's District Offices, Office of General Consul, and the Office of Compliance in the review of manufacturing records, product complaints and adverse event reports obtained by FDA. I was the primary clinician involved in several of FDA's Major Corporate-Wide actions for which I received various citations and honors for my services from FDA, including Department of Health and Human Services and the Federal Government Employee of the Month.

I was sent by FDA as official Agency representative to medical meetings and seminars to help monitor medical device manufacturers and distributors for deviations from regulations governing promotional activities. I was also required to provide guidance as to the FDA's interpretation of Food and Drug Laws as they pertain to medical products and the role of manufacturers.

After leaving FDA, and founding Medical Device Assistance, Inc., I have continued to provide information to individuals and organizations outside FDA regarding FDA's requirements, Adverse Event Reporting, and labeling of medical products. I was requested by FDA to participate in a 1997 panel of experts convened by FDA to comment on changes proposed in the requirements for medical device labeling. I continue to lecture at conferences and seminars regarding FDA, premarket clearance, design of clinical trials and product labeling. I am the author of FDA Inside and Out published May 2001 which is a book about the workings and history of the FDA.

II. Information Considered

My opinions are based upon my own personal experience and knowledge of activities developed while at the FDA, my review of FDA's records, my own professional activities, education and experience, and consulting activities after leaving FDA. I am familiar with the FDA's regulation of medical products, including radiological and imaging products, Adverse Event Reporting, health risk assessment, and labeling of FDA-regulated products that are intended to be marketed in the U.S. I have been responsible for the Agency's review of biocompatibility and toxicity data including animal and clinical studies. I was Chief Medical Officer of ODE's Division that reviewed radiologic products and was involved in the review and evaluation of contrast agents

and imaging devices. I am a Board Certified Anatomic and Clinical Pathologist.

I have reviewed materials regarding Iophendylate, Pantopaque, Lafayette Pharmacal, Eastman Kodak Company, Alcon Laboratories, Inc. that have been provided to me for this litigation. I have conducted my own review of FDA's database and the U.S. medical literature through the National Library of Medicine's database to obtain documents pertaining to the use of iophendylate. I have reviewed all the Iophendylate, Pantopaque and Lafayette Pharmacal, Inc. and Alcon Laboratories, Inc. documents that were available to me within the public database. Finally, I have reviewed the March 20, 2002 Expert Witness Report of Charles V. Burton, M.D.

III. FDA's Approval of Drugs - A Brief Overview

1930's

FDA's regulatory premarket oversight was officially extended over human drugs sold in the United States following the passage of the 1938 Food Drug and Cosmetic Act (FDCA) signed into law by President Franklin D. Roosevelt. Among the many provisions of the 1938 FDCA, was the requirement that all new drugs be required to be shown through FDA's approval of a premarketing submission that they were "**safe**" before being legally allowed to be marketed in the U.S. The results of safety testing would be submitted to FDA in a New Drug Application (NDA) This revision of the earlier 1906 Act also had a provision that any drug which was marketed prior to June 25, 1938, could continue to be marketed without FDA's approval provided no significant alterations in formulation or labeling had occurred since that time. That is, such a drug would not be considered a new drug (i.e. grandfather clause.)

The law also required that drugs have adequate labeling for safe use. The monitoring of all drug advertising was assigned to the Federal Trade Commission.

1940's

The early 1940s saw three major additions to FDA's responsibilities in terms of drugs. The Insulin Amendment, passed in 1941, required all batches of insulin to be tested for purity, strength, quality, and identity before marketing. Also starting in 1941, the Agency required prescriber labeling for all new drugs in concert with the adequate directions for use provision of the 1938 Act. The Penicillin Amendment was passed in 1945, modeled on the Insulin Amendment. The former required batch certification of drugs wholly or partially composed of penicillin. Subsequent amendments extended the certification requirement to other antibiotics.

The FDCA and World War II greatly expanded the role of FDA's overall regulatory oversight. Wartime demands stimulated the rapid development, availability and marketing of new "wonder drugs", especially antibiotics for treating war casualties.

(* Pantopaque was approved for marketing 1944 through support of "safety".)

1950's

At the start of the 1950's, FDA's resources were still viewed by Congress and the Agency as seriously deficient for the assigned tasks. FDA's appropriations and staff in the 1950's, never considered as adequate by Congress, had remained approximately at the same levels as 1938 when Congress passed the FDCA. The 1951 Durham-Humphrey Amendment to the FDCA further defined U.S. drugs that could not be safely used without medical supervision and restricted the sale of these drugs to receipt of a prescription by a licensed health care provider.

In 1955, FDA undertook a pilot study on adverse drug reaction reporting. In cooperation with the American Society of Hospital Pharmacists, the American Medical Association, and others, the study was focused on reactions that could be reported by hospitals and pharmacists. Adverse reaction reporting was voluntary and reports were usually scarce. This study blossomed into a more ambitious effort in 1957 to test a large-scale system for voluntary reporting to assist with post-marketing evaluation of new drugs. By 1963 the study had evolved into a voluntary reporting system with almost 20 hospitals participating.

1960's

In Europe, there was a major safety uproar secondary to the disastrous introduction of the drug thalidomide, a new sleeping pill, and its subsequent association with a production of serious birth defects. However, the United States's FDA was viewed in a positive light after the cautious actions of FDA's Medical Office **Dr. Frances Kelsey**, that had kept the drug from approval for commercial entry onto the U.S. market. Despite lack of FDA approval, more than two million thalidomide tablets had been distributed in the U.S. as "investigational drugs". Investigational drug distribution had been largely unregulated in the US under FDCA.

The FDA's prudent actions to not approve thalidomide that appeared to have protected US public safety aroused a strong public support for FDA's role in drug regulation and the need for stronger laws to ensure "drug safety". In partial response to the issue, FDA's Commissioner George Larrick established an Advisory Committee on Teratology and Congress was able to obtain the necessary public support to pass the 1962 Kefauver-Harris Drug Amendment to ensure drug "safety and efficacy".

The **1962 Kefauver-Harris Drug Amendments** or the Drug Amendments of 1962 to the FDCA continued to require that a "new drug" be required to demonstrate that it was both "safe" but also now that it was "effective" before being allowed commercially onto the U.S. market. As a result of the 1962 Amendment to the FDCA, FDA also retrospectively went back to reassess the "efficacy" of nearly 3,000 prescription drugs that FDA had already allowed to be introduced onto the U.S. market between 1938 and 1962. (*That review included Pantopaque.)

The FDA responded to this large retrospective review task given to it by Congress by seeking external advice or assistance through a contract with the National Academy of Sciences- National Research Council (NAS-NRC). NAS-NRC membership were required to review previously marketed prescription drugs and made recommendations to FDA regarding safety, efficacy, and

labeling. The FDA's retrospective efficacy review program was called the "**Drug Efficacy Study Implementation Review**" or "DESI".

As a result of DESI, in the years following 1962, literally thousands of previously "approved" drugs were removed from the U.S. market by FDA because it was determined that they lacked evidence in the medical literature to support "efficacy". DESI evaluated 3000 separate drug products and over 16,000 therapeutic claims. By 1984, FDA had completed final action on 3,443 products; of these, 2,225 were found to be effective; 1,051 were found to not be effective, and 167 the decision was still pending.

FDA also required manufacturers to update their product labeling to reflect the known medical facts regarding drug safety and efficacy determined by DESI and to bring drug labeling into compliance with FDA's requirements for prescription labeling. Drug prescription labeling was revised to be more uniform and come into compliance with FDA's prescription labeling requirements of the FDCA and labeling for other similar products. To expedite developing drug prescription labeling for similar types of products, FDA turned to the regulated industry itself for models of the "best" designed labeling for each type of product.

The 1966 Fair Packaging and Labeling Act required all consumer products sold in interstate commerce to be honestly and informatively labeled. FDA became officially responsible for enforcement of labeling provisions for foods, drugs, cosmetics and medical devices.

(*Pantopaque had been approved with "safety" data in 1944, and was included in the FDA's retrospective drug review (DESI) of the medical literature by NAS-NRC for support of both safety and efficacy. FDA required labeling changes that coincided with NAS-NRC medical literature review and labeling of similar products.

In 1963 FDA had required the sponsors of Pantopaque to submit a new NDA for gaining approval of a new strength (15% iodine) Pantopaque, or Pantopaque II. The product for the new NDA would be required to meet the Agency's new requirements for animal safety testing to assure safety, scientific support of both human safety and efficacy, requirements further developed by FDA since the initial World War II era NDA for Pantopaque I (30% iodine). The new Pantopaque NDA was subsequently left uncompleted and withdrawn by Lafayette Pharmacal in 1969.)

1970's

In *Upjohn v. Finch*, 1970, the Court of Appeals upheld enforcement of the 1962 Drug Efficacy Amendments by ruling that commercial success alone did not constitute substantial evidence of drug safety and efficacy. FDA's review actions of drugs for "efficacy" had been curtailed while the Agency waited to learn the final decision of the Courts as to legality of the Agency's enforcement actions for "efficacy" requirements.

A 1977 Intercenter FDA Task Force established a Bioresearch Monitoring Program for FDA. The need for such a program to monitor clinical trials became evident from a survey of the

"conductance of clinical studies" involving FDA-regulated products by FDA's field inspection operation team between 1972 and 1974. Following a further review of the agency's inspectional findings, Congress mandated that FDA immediately develop and implement a new agency-wide program for monitoring the conductance of bioresearch and clinical activities.

1980's

In 1982, the Bureau of Biologics and the Bureau of Drugs were merged into a Center for Drugs and Biologics, with Biologics products regulated through the Office of Biologics. In 1987 the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) officially were divided into two separate and independent FDA review and evaluation Centers.

1990's

As a result of the U.S. push to obtain cheaper generic drugs and the FDA's Generic Drug Scandal of the 1990's, (*i.e. manufacturers had supplied FDA with fraudulent data regarding the production of generic drugs), the FDA instituted product-specific, pre-approval inspection of manufacturing sites listed within a sponsor's marketing applications would extend to generic drug applications. During pre-marketing approval inspection, FDA was required to review the step-by-step manufacturing process of each product under review. All drug applications were reviewed for their scientific content and for manufacturing procedures as well as validation methods, raw material specifications and container and closure systems used.

By **Federal Register**, September 10, 1991, **FDA's Notice 56 FR 46191- Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities; Final Policy**, the agency announced its final policy that set forth FDA's approach regarding applicants that sought to subvert the agency's review and approval process of premarketing applications.

2000's

CDER 06/19/00 release of the **Guidance for Industry- Developing Medical Imaging Drugs and Biological Products**. This guidance was prepared by the Division of Medical Imaging and Radiopharmaceutical Drug Products in CDER and the Office of Therapeutics Research and Review in CBER, FDA, with comment from Office of Device Evaluation, Radiological Branch, CDRH. The guidance was to represent the Agency's current thinking on the development of medical imaging drugs and biologics (*medical imaging agents*).

IV. "PANTOPAQUE"

A. Early Development

Approximately 1918, following a proposal by Dandy, visualization of the spinal cord radiographically was done by injection of air into the spinal column to enhance anatomic

structure imaging. In 1922, iodinized poppy seed oil, which had been commercially available since 1901 for injection into the epidural space, began to be used for intrathecal injection for enhanced imaging of the spinal cord. Usually less than **5 cc** of poppy seed oil was introduced into the intrathecal space and it was recommended that it be removed following imaging. A **1932** opinion statement of the **American Medical Association** had discouraged the introduction of any foreign oily material, such as iodinized poppy seed oil, into the spinal cord unless the potential benefit of the procedure could justify the potential long-term risk to the patient.

The investigation of the use of the medical imaging agent ethyl iodophenylundecylate, which would eventually be called Pantopaque, began in 1936 at the University of Rochester, School of Medicine and Dentistry, Rochester, NY with initial animal work done by William Strain, Ph.D. and Stafford Warren, MD. The investigators were reportedly seeking a more effective and safer medical imaging agent for imaging the spinal cord then iodinized poppy seed oil. They also wanted to develop a radiopaque substance that would be nontoxic when injected into the spinal canal, that would disappear from the body within several weeks, more rapidly then the iodinized poppy seed oil, and also improve the overall quality of radiological imaging of the spinal cord.

They began working with several different oily iodinated compounds. During animal studies in 1937-1938, Warren and Strain began referring to one of their new oily iodinized non water soluble medical imaging agents as ethyl iodophenylundecylate, iophendylate, or "Pantopaque". Their animal studies indicated that the oily imaging compound was <u>not</u> absorbed by the body and, just as with the already available oily non water soluble iodinized poppy seed oil, would remain permanently encysted within the spinal column as a foreign body capable of triggering a moderate inflammatory reaction with production of fibrosis.

The June 1941 doctoral thesis of T.B. Steinhausen, also at the University of Rochester and who was working with Strain and Warren, a study funded for the Radiopaque Group by Eastman Kodak Company, was entitled "An Experimental Study of Iodinated Compounds for Intrathecal Use". His work involved the use of rat and dog animal studies and a series of iodinated imaging compounds. The potential contrast media of his thesis, Pantopaque, had been a product synthesized by Plati in 1940.

Steinhausen began his thesis work by looking at the intrathecal injection effects of the already available iodinized poppy seed oil (or Lipidol) in animal systems. It was his opinion that since there had been no histological tissue information available with very little experimental studies done regarding the nature of the foreign body reaction stimulated by the material when injected into the human's subarachnoid space that it should not be considered as a suitable product for human use. He reviewed cat studies that demonstrated there was no absorption of the iodinized poppy seed oil over time and that one of the cats had died following injection. He commented that those researchers appeared to have used too much oil in that cat and that there was no way that iodinized poppy seed oil should ever be considered as safe for human injection.

Steinhausen cited an earlier 1925 rabbit study using 17 rabbits with intrathecal Lipidol injection that had a 47% mortality with pathological changes seen at autopsy. He referred to a 1938 study by Mettier and Leake that had reported numerous untoward reactions secondary to the

introduction of iodinized poppy seed oil into the intrathecal space. For this reason, Steinhausen stated that those authors had recommended that the oily iodinized poppy seed agent be used very carefully and that every effort should be made to remove as much of the substance as possible immediately from the intrathecal space following an imaging procedure.

He cited that in 1939, Brison had developed a technique that would aid in removal of iodinized poppy seed oil from the subarachnoid space in order to help decrease the potential meningeal irritation. This was a procedure that was similar to a procedure used at the Mayo Clinic. A 1941 study by Brown and Carr, following a 6 month instillation of retained intrathecal injection of poppy seed oil, had found the oil emeshed or encysted within fibrous adhesions in the spinal column amongst a thickened dura with chronic inflammation. The authors also had indicated that there was a significant danger in injection of iodinated poppy seed oil within the spinal canal for imaging.

One of the new iodinated compounds that was studied by Steinhausen in his thesis included ethyl iophenylundecylate ("Plati's iophendylate" or "Pantopaque"). This compound was reportedly chosen by Steinhausen because it would break down more slowly than the other iodinized agents that he examined. That property was one that he thought would help facilitate better radiographic imaging.

In a series using 3 dogs, Steinhausen's Pantopaque produced meningeal irritation symptoms that ranged from slight to severe. In another series of 15 dogs all injected intrathecally with 4 cc Pantopaque, 27% were clinically free of meningeal irritation symptoms, 46% had symptoms of slight meningeal irritation at 2-9 days, 20% had moderate symptoms at 3-9 days, 7% had severe meningeal irritation symptoms beginning at day 4 and lasting 12 days, with 1 dog dying on the 24th day post-injection from a gangrenous terminal ileum.

In the dog studies, despite a lack of overt acute clinical symptoms, at time of termination of the study and autopsy, the histological and gross meningeal changes were more severe in nature then had been clinically suggested. Such significant changes included granulomatous foreign body reactions with acute inflammation, polymorphonucleocytes (PMNs), phagocytes, and fibroblasts with fibrous adhesions involving the nerve roots. The typical meningeal histological changes seen at dog sacrifice at 1½ months post intrathecal injection included clear cystic areas, dispersed throughout the spinal column, consistent with the presence of pockets of retained oily injected material, surrounded by fibrosis, scattered macrophages and acute inflammation.

One of Steinhausen's 15 Pantopaque dogs following injection had a persistent generalized weakness of the legs with an inability to walk. This was the first time that this type of generalized neurological reaction with lower limb paralysis had been reported by Steinhausen associated with the use of any of the oily imaging compounds that he was testing.

For the purpose of comparison and using his model, Steinhausen injected a series of 9 dogs with iodinized poppy seed oil. One dog died 24 hours after injection, with symptoms of moderate meningeal irritation and subarachnoid hemorrhage. 80% of the dogs appeared to recover clinically without remaining neurological symptoms. However, histologically, at time of

termination and autopsy, the histological and gross changes were similar to the changes that had been seen with injections of ethyl iophenylundecyalate (Pantopaque) and the findings were more severe than would have been suggested clinically. The primary difference for the iodinized poppy seed oil, when compared to Pantopaque in the dog model, was that the iodinized poppy seed oil appeared to produce greater number of clinical symptoms referable to the immediate mechanical trauma of the injection. Histologically, the iodinized poppy seed oil resembled the changes produced by Pantopaque, including moderate meningeal irritation with areas of oil floating within the cord as encysted clusters, acute inflammation, fibroblasts, fibrous adhesions and nerve root involvement.

Steinhausen's research in dogs foreshadowed both the significant acute and long-term adverse events that were reported in human patients following the intrathecal injection of Pantopaque for myelography. In terms of the body of Steinhausen's research, it is unclear why, in lieu of the significant and severe animal safety findings produced by intrathecal administration of Pantopaque, and the similarity to the harmful effects of iodinized poppy seed oil, that he would have made the following 4 thesis conclusions regarding the apparent imaging "utility" of Pantopaque for injection into humans for myelography:

> 1. Of the 26 ethyl esters of various iodinated organic acids, only ethyl iodophenylundecylate seemed suitable for myelography.
> 2. Ethyl iodophenylundecylate appeared to be absorbed and as long as any of the ester was present there was some pathological reaction about the compound.
> 3. Comparative tests with the standard iodized poppy seed oil showed a definite but different pathological response which persisted indefinitely, since the compound was very slowly absorbed.
> 4. Ethyl-w-(4-iodophenyl)-o-valerate, although not suitable for myelography, had found clinical application as a contrast medium.

Despite the documentation by Steinhausen of the similarities and risks of Pantopaque when compared to Lipidol in animal studies, despite the 1932 warning of the AMA regarding the permanent long-term risks for introduction of foreign oily compounds into the spinal cord for imaging, and despite the FDCA's 1938 requirements for obtaining FDA's premarketing approval through demonstration of "safety" to the FDA before introducing an imaging agent for use in U.S. patients, Dr. Warren took it upon himself to begin sending Pantopaque to U.S. physicians to obtain their clinical input from imaging their own patients. The 1938 FDCA, as seen with the later distribution in the U.S. of two million of investigational tablets of thalidomide in the early 1960s, did no address the legal responsibility of a manufacturer to control the distribution of "investigational drugs", nor did it require obtaining informed patient consent or obtaining an Investigational New Drug (IND) exemption from FDA.

On June 26, 1942, Dr. Rigler, University of Minnesota Hospitals, Minneapolis, MN, wrote to Dr. Warren reporting his facility's negative clinical experience with Pantopaque for imaging their patients. Dr. Rigler did not provide "favorable" information to Dr. Warren regarding the performance of Pantopaque in human patients. Dr. Rigler indicated that it was his opinion, as well as his staff's opinion, that the material mixed too readily with the spinal fluid and <u>did not</u>

improve imaging quality. He also indicated that he felt that the material was extremely difficult to remove. Dr. Rigler wrote to Dr. Warren of the experiences of his staff with Pantopaque:

> We have completed some myelographies with your Pantopaque which you were so kind to send me, but for our purposes we have found it somewhat unsatisfactory. Doctor Peterson, who has been doing this work here for some time and has had a considerable experience with both air and lipidol, feels that the material mixes much too readily with the spinal fluid so that a clear cut picture cannot be obtained. Obviously, in a case of a block of any degree, it would be entirely satisfactory, but if you are trying to demonstrated herniated disc or tumor without complete block or arachnoiditis, the normal miscibility of the material would be most confusing.
>
> Furthermore, he found it extremely difficult to remove. Large quantities of spinal fluid were removed by the usual methods that we use in removing lipidol, but he was quite unsuccessful.
>
> I am sending you illustrations of two cases, one done with lipidol and the other with Pantopaque, to give you some idea of the contrast, both the original films and the amount of opaque material left after attempts at removal. You will note that in the case of lipidol, using the maneuver of Kubik and Hampton, all except a very few droplets were successfully removed whereas in the case of the Pantopaque most of it all remained.

From other documentation, Dr. Warren had also sent Pantopaque to physicians based at military hospitals to encourage their use of the product for imaging military patients. Major R.G. Spurling, Walter Reed Hospital, Washington, D.C., September 5, 1942, wrote to Dr. Warren in 1942 indicating that Pantopaque produced as many irritative symptoms as lipidol (poppy seed oil) but it was absorbed more rapidly. When removed immediately post procedure, there had been no more evidence of meningeal irritation than after a plain lumbar puncture. Major Spurling felt 90-95% of the Pantopaque could be removed, with the remainder absorbed in two to four weeks. Major Spurling had observed a patient of his that he had injected a **5cc** dose of Dr. Warren's Pantopaque material intrathecally and concluded that approximately 50% (*2.5cc) had been absorbed at the end of 7 months by serial x-ray. He also wrote:

> When Pantopaque is removed immediately following the myelogram, there is no more evidence of meningeal reaction than after plain lumbar puncture studies. Furthermore, with ordinary care, it is possible in all cases to remove 90 to 95% of the Pantopaque from the subarachnoid space. A few drops remaining cause no demonstrable clinical signs and these droplets are absorbed within two to four weeks.
>
> I have used Pantopaque in approximately one hundred clinical cases and I consider it to be the most nearly ideal myelographic medium yet available.

September 16, 1942, eleven days after Dr. Spurling's letter had been written to Dr. Warren, FDA

responded to an earlier September 4, 1942 letter received from Mr. J.T.Fuess of Chemical Sales Division, Eastman Kodak Company, Rochester, NY, regarding the issue of Eastman Kodak's reported interstate deliveries of Pantopaque. The letter was written by the Assistant Commissioner of the FDA, P.B. Dunbar.

> This refers again to your letter of September 4 in reference to Pantopaque. With the understanding that deliveries of this drug will be restricted exclusively to the military forces,(*Underlining added for emphasis.), this Administration will not insist on compliance with the requirements of section 505 of the Act dealing with new drugs.
>
> Should you contemplate at any time entering into the ordinary commercial distribution of Pantopaque, it will be expected that the precise requirements of section 505 of the Act will be met. This will require the filing of a formal application with proof of the safety of the drug. If in lieu of filing of a formal application you elect to take advantage of section 505(i) and distribute the drug solely for investigational use by qualified civilian experts, it will be expected that the requirements of section 505(i), together with the regulations thereunder, will be met, including the labeling of the product with the statement "Caution: New drug-Limited by Federal law to investigational use."
>
> Up to the present time we have had inquiries regarding the use of Pantopaque only from the Office of the Surgeon General of the War Department. Should a similar request be received from medical authorities of the Navy our decision would be identical.

However, in apparent violation of the " military-only restrictions" stated in the FDA's letter for legal distribution of the drug to military facilities, **December 1, 1942**, Dr.s Steinhausen, Plati, Furst, Dungan, Smith, Strain and Warren presented the results of their "Experimental and Clinical Myeolography with Ethyl Iodophenylundecylate (Pantopaque)" at the 28th Meeting of the Radiological Society of North America, a "civilian medical association".

The data began with a presentation of results of intrathecal injection of 3-5cc in dogs. However, the presentation concluded with an **open "off label clinical discussion"** of the use of their "**unapproved**" contrast agent in three unusual clinical cases, with no mention of FDA's restriction to military-only use. There was no mention within the written abstract that product availability had been "restricted" by FDA to military medical facilities, nor was there a discussion that the "safety" for human use had never been submitted nor demonstrated to the FDA for support of marketing the product for use in a US human population.

In terms of the sponsors' Pantopaque presentation in the abstract, it also appeared that the authors did not wish to accurately reflect the earlier Steinhausen dog data nor actual clinical experience described in the 1942 letter from Dr. Rigler in terms of his facility's "unfavorable" clinical experience. There appears to have been a conscious decision in 1942 by the authors to disregard Dr. Rigler's clinical findings, an intentional disregard of the requirements that had been detailed by the FDA, an intentional disregard of clinical ethical conduct, and failure to provide physicians

with complete and accurate, and truthful outcomes documented for Pantopaque through both human and animal experience. The abstract misrepresents the scientific facts for Pantopaque as known by the authors in 1942 by containing "misleading" statements about the long-term effects of Pantopaque in the dog studies:

> The new medium is more fluid than the iodinized oils and may be injected with ease. With dogs intrathecal injection of 3-5 cc causes a **transitory** pleocytosis with cell counts of 200 to 700 (mostly polys). Histological sections taken during or after this **transient** reaction period show collection of the medium under the meninges with a **localized foreign body response** around the small droplets. Consecutive radiographs demonstrate that the preparation is **rapidly absorbed at first**, but more slowly as the medium becomes fixed in position. Nevertheless, amounts of **3-5 cc** are absorbed **nearly completely in the course of a year with little or no evidence of residual reaction.** Parallel experiments with iodized poppy seed oil in dogs show somewhat **more extensive pathology** with little evidence of absorption. Clinically, the new medium has been found to **facilitate greatly myeolographic examination**. In addition to ease of injection, the preparation flows readily immediately after injection and **may be removed without difficulty**. The entire examination, including injection and removal, can be completed in fifteen minutes.
> (*Bold added for emphasis)

B. Pantopaque, FDA and New Drug Approval (NDA)

November 4, 1943, Lafayette Pharmacal Company submitted **NDA # 5-319** to FDA to obtain the Agency's premarketing approval of the imaging agent, Pantopaque, intended for myelography in US population based on the support of safety. Prior to the NDA submission there was an Agency memo of a telephone conversation that had occurred between Dr. Walton VanWinkle, MD of FDA and Dr. Strain of University of Rochester, Rochester, NY. Dr. Van Winkle had requested that Dr. Strain provide **animal safety data** that could support the safety of Lafayette Pharmacal's NDA.

> Dr. Strain stated that he had received copies of our correspondence with the Lafayette Pharmacal Company with reference to the new drug application for "Pantopaque".
>
> He stated that he would furnish them with data relative to animal experiments which he had performed. He stated that he did not have very good figures on the acute toxicity and felt that the obtaining of any adequate data with regard to intrathecal injection would be difficult. He was told that he should submit all the data which he could obtain and should certainly give us some sort of reliable figure for at least the intravenous toxicity. He was also told that we would like to have some comparison between chemical meningitis produced by pantopaque and the reactions produced by lipidol. He stated that he felt he had sufficient data on this to answer our questions.

> Dr. Strain said that Dr. Spurling was publishing a resume of his experience with this preparation in the August issue of the Army Medical Bulletin. As soon as reprints are available copies will be sent to us.

Apparently, trying to obtain a response to the Agency's request for animal data, there followed a February 22, 1943 letter to Dr. Warren authored by Dr. H. Hodge, Professor of Biochemistry and Pharmacology, University of Rochester, regarding his **acute toxicity studies** of Pantopaque conducted in the mouse model.

> I have examined the acute toxicity of ethyl iodophenylundecylate (Pantopaque) and have determined that the amount required to kill the average mouse is in the order of **4.6.gms** of Pantopaque per kilogram of body weight of the mouse. The Pantopaque administered intraperitoneally. These data indicate that Pantopaque is only moderately toxic. It has about the same order of toxicity as sodium chloride has. The appearance of hemorrhage in the intestine is unusual and probably represents a specific toxic action of Pantopaque. However, the doses given the mice were relatively huge as compared to the doses which will be employed clinically.

Dr. Hodge's limited animal toxicity data had not developed a **Lethal Dose 50** for intrathecal pantopaque-(i.e. the amount of drug that will produce a 50% mortality in the animal species being examined.) Dr. Hodge's data indicted his estimated amount of Pantopaque injected intraperitoneally that would be "lethal" to the average mouse. From later reports by Dr. Strain, acute and chronic animal toxicity studies were conducted using Pantopaque at the University of Rochester and the data supplied to Lafayette Pharmacal to forward on to the FDA in the NDA. In the mid 1960s FDA found these same animal studies inadequate to support Pantopaque safety.

The documentation I have available for NDA 5-319 contains a 5 page Statement of Directions (* identified as revised -1944) for physicians. This provides an initial example of Lafayette Pharmacal's proposed labeling for Pantopaque as the firm intended to marketed the imaging agent to physicians in the U.S. in 1944.

The Pharmacology section stated that:

> Pantopaque is absorbed in about 6 weeks from the peritoneal cavity of experimental animals when injected at the level of 4 gms or less per kilogram, and is absorbed in about 15 months from the subarachnoid space of dogs when administered in a dose of 3 cc per animal. Because the medium is absorbed, there is associated a moderate toxicity. Thus the dosage which causes death in 24 hours in 50 percent of experimental animals (LD 50) has been found to be: 4.5 g/kg. When injected intraperitoneally in mice, 19 g/kg. When injected into rats, and 2.1 g/kg. When administered orally to rats. Death in these lower orders is accompanied by moderate fatty degeneration of the liver and minor pathology of the kidney. No toxic phenomena have been observed, however, following intrathecal injection into rabbits and dogs even when massive doses have been administered. In agreement with this, reports from **several thousand myelograms** (* bold added for emphasis) in which **2-**

5 cc (* bold added for emphasis) of the medium has been used show that Pantopaque is well tolerated even **when left** (* bold added for emphasis) in the spinal canal. In those cases where the bulk of the contrast medium has been removed using the technique of **Kubik and Hampton**(* bold added for emphasis) , the small amount of material that is left is usually absorbed within 2 months. Where none of the medium is removed the absorption proceeds at a variable rate depending on conditions within the spinal canal, and may require years.

The Injection of Pantopaque section indicated:

A previously prepared 5 cc. Syringe containing **2-5 cc.** of Pantopaque is then secured to the adaptor of the needle, and the medium is injected slowly into the subarachnoid space....When the Pantopaque has been injected, the syringe is detached from the needle and the stylet replaced. A sterile gauze dressing is then placed over the adaptor of the needle and the patient is ready for the examination.

In the 1944 proposed NDA draft labeling, Lafayette indicated to FDA that the proposed dose of Pantopaque administered for myelography was " **2-5 cc".**

Removal of Pantopaque section stated:

....It should be possible to remove 80 percent to 90 percent of the injected Pantopaque without much difficulty.....

Side Effects section stated:

Clinical reports indicate that the incidence and the severity of the side effects following Pantopaque myelography with aspiration of the medium **is but slightly greater than with ordinary lumbar puncture.**(* bold added for emphasis) In 10-30 percent of such cases there may be transient asymptomatic reactions consisting of slight temperature elevation and increase of symptoms referable to a back condition.

When the medium is not removed, **similar transient side effects** (* bold added for emphasis) occur with a slight elevation of temperature in a greater percent of patients. To reduce the reactions to a minimum and to facilitate absorption of the medium, the bulk of the Pantopaque should be removed by aspiration after myelography.

The Limitations section for the use of Pantopaque stated:

Pantopaque has not been studied adequately from a clinical stand point as a contrast medium for body cavities other than the subarachnoid space. The limitations and contraindications in other areas are not known.

The NDA also included information about a proposed dog study protocol, with no population size provided,(* Appears to represent the proposed assay method for ensuring the batch quality of the manufactured material prior to release of the material for sale by the University of Rochester, School of Medicine and Dentistry, and prior to distribution by Lafayette Pharmacal.). The protocol indicated that at least 5 dogs were to be injected in any one assay and at least 3 of

these 5 should not develop "fevers" greater than 1.5 C. lasting longer than 2 days.)

In the materials I have reviewed from Lafayette Pharmacal, there is a November 15, 1943 **Radiopaque Group Report** generated by Dr. W. Strain regarding the current status of the radiopaque compounds that he was investigating at University of Rochester from August-November 1943. This information was not apparently intended for submission to FDA within the NDA. In terms of the agent Pantopaque and Dr. Strain's update report:

> The data relating to the physiological properties of Pantopaque have been submitted to the Lafayette Pharmacal Inc. This material has also been discussed informally with the Food and Drug Administration.

Dr. Strain continued his discussion regarding the new agent Atriopaque:

> Physiological assays show that ATRIOPAQUE, a viscous liquid contrast medium, has about the same toxicity as PANTOPAQUE and is absorbed at about the same rate.

In his final discussion he stated:

> During the period August-November, 1943, emphasis has been on the physiological study of the four products designated as Pantopaque, Atriopaque, Cholopaque and Gastopaque III. This has been carried out at the Medical School with the assistance of W.R. Chaleaxe, MD and Leon Miller, Ph.D. both of whom have assisted on a part time basis. In connection with this work it has been necessary to have added supplies of the radiopaque compounds, and these have been prepared either by Dr. Creseman, working in Dr. Allan's laboratory, or by Dr. Hartman. The work has been seriously handicapped by an acute shortage of rats and rabbits; steps are being taken to assure a more satisfactory supply.....
>
> The material relating to <u>acute and chronic toxicity</u> (* underlining added for emphasis) has been collected for the Lafayette Pharmacal Inc. and submitted to them under the following headings:
>
> 1. Provisional Specifications for Ethyl Iodophenylundecylate (PANTOPAQUE)
> 2. Acute Toxicity by Intraperitoneal Injection of Mice
> 3. Acute Toxicity by Intraperitoneal Injection in Rats
> 4. Acute Toxicity by Oral Administration in Rats
> 5. Acute Toxicity by Intravenous Administration to Dogs and Rabbits
> 6. Acute Toxicity by Intrapleural Injection in Dogs and Rabbits
> 7. Chronic Toxicity by Intraperitoneal Injection in Various Species
> 8. Chronic Toxicity by Intrathecal Injection in Dogs
> 9. Chronic Toxicity by Intrathecal Injection in Rabbits
> 10. Chronic Toxicity by Intra-Alveolar Injection in Dogs
> 11. Chronic Toxicity by Intra-Uterine Injection in Rabbits.

> Copies of these have been filed with Mr. Fuess together with the material relating to the chemical preparation and the clinical testing of PANTOPQUE which was submitted to the Lafayette Pharmacal during the spring. A master copy has been retained in the Department of Radiology.
>
> When all these reports were available, they were discussed on October 20 with Dr. Walton Van Winkle, Jr. at the Office of the Food and Drug Administration. Dr. Van Winkle expressed the opinion that the drug had been adequately studied and that as soon as the reports had been officially submitted to him, steps would be taken to consult with the investigators who had used it. Van Winkle revealed however, that the Food and Drug Administration was short-handed and that the investigation may take time. In the course of this interview it developed that the Food and Drug Administration would make no attempt to police the manufacture of PANTOPAQUE since it will be made by one manufacturer and distributed through one pharmaceutical house. He further disclosed that the Army and Navy acted independently of the Food and Drug Administration and that any dealings with the services were free of the restrictions which are imposed on new drugs for civilian use.

November 18, 1943, Lafayette Pharmacal's Mr. W.S. Bucke wrote to Dr. Van Winkle, Jr. of FDA the following letter supplying the additional data obtained from Dr. Strain:

> In reply to your request of November 9, 1943, we are pleased to enclose herewith data suggested for circular setting forth the indications, dosage and contraindications for PANTOPQUE in addition to the "Technique for Myelography with Pantopaque". With this additional data we hope that the Department will be in a position to act upon our application.

January 21, 1944, Dr. Van Winkle of the FDA wrote back to Mr. W.S. Bucke. FDA had the following concerns regarding approval of the Pantopaque premarketing application:

> Further consideration has been given to your application under section 505 of the Federal Food, Drug and Cosmetic Act for the preparation of "Pantopaque". From the description of control procedures contained in the application, we are somewhat in doubt as to the extent of the test to be made on each batch of the drug. In discussing the preparation of the active ingredient, we note that certain physical constants are mentioned and the drug is assayed biologically in dogs. It also appears that a total iodide content determination is made. We assume that these examinations are to be made either by the Eastman Kodak Company or by the University of Rochester. It does not appear that you exert any chemical control over the drug after you receive the raw materials. In our opinion, it will be highly desirable for some further check to be made on the finished packaged product. We , of course, are not in the position to state what sort of a test is most desirable, but we feel that the manufacturer should assure himself that the product, before distribution

in the channels of commerce, meets the criteria for quality and purity as specified in this application. It is also suggested that in addition to the tests proposed in the application, a test for free iodine is included. This is particularly desirable in that no information has been furnished concerning the stability of this product, other than the fact that the color changes on exposure to light.

The clinical reports which have been submitted leave one with the impression that a rather **large number of reactions of varying degrees of severity have been observed** (* Bold and underlining added for emphasis.), with the use of this material. We are aware that some of these reactions may be accounted for by the fact that the investigators failed to remove the material following examination of the patient. However, on the basis of the reports contained in the application and without additional data, **we hesitate to permit this application to become effective on the basis of safety for use** (* Bold and underlining added for emphasis). It is suggested that additional reports be obtained from some of the investigators mentioned in the application to whom material has been sent but who have not submitted reports. We would be particularly interested in having them state their opinion of the safety of this preparation as compared to lipidol and to discuss the nature and severity of the reactions observed by them as compared to those observed when lipidol is used.

In our opinion, the proposed circular setting forth the indications and method of administration of this product is **not wholly satisfactory** (* Bold and underlining added for emphasis). Because the **severity of reactions** (* Bold and underlining added for emphasis) observed in patients in whom the product is not removed after injection, we feel that **considerable stress** (* bold for emphasis) should be laid upon the necessity for removing this material on completion of the radiologic examination. It might be well for the label of the product to bear a caution calling this fact to the physician's attention. **The entire circular creates the impression that reactions are infrequent and are of a minor character.**(* Bold and underlining for emphasis) The reports which have been submitted do not confirm this impression. We suggest, therefore, that a more thorough discussion of the side reactions and potential toxicity be given in the circular and that it be stressed that these reactions **appear almost uniformly if the product is not removed following examination** (* Bold and underlining for emphasis) of the patient. It is also suggested that the circular state that the product is **not intended for use in the bronchi or in the uterine cavity.**(* Bold and underlining for emphasis)

At the time you submit the additional data regarding controls and toxicity, you should submit a draft of the proposed revised circular and labels.

February 5, 1944 Lafayette Pharmacal, Inc. sent a NDA Supplement to FDA including physical and chemical testing properties, and the biological assay method using dogs. The supplement included the animal studies previously listed in the earlier Dr. Strain **Radiopaque Group Report** summary. The data included the acute and chronic toxicity testing of injected

intraperitoneal experimental batches of Pantopaque in rats, mice, rabbits and dogs including intra-uterine injection in rabbits with comparison to iodinized poppy seed oil; intrathecal injections of rabbits; intra-alveolar injection of dogs, intrathecal injection of dogs. In the dog studies, histological sections of dog spinal column continued to demonstrate encystation of the retained iodinized oil- whether the substance was iodinized poppy seed oil or pantopaque. The cysts of retained iodinized poppy seed oil were generally larger than the multiple small scattered cysts of Pantopaque. There were acute toxicity studies with rats involving oral administration of Pantopaque.

The supplemental NDA information included a clinical report generated by Dr. W. Hagman(?), Neurosurgery Dept., University of Rochester School of Medicine. The clinical report involved his experience with 30 patients undergoing imaging of a suspected spinal cord space displacing mass (*tumor). The report consisted of an abstract that had been presented May 19, 1942 at the New York Meeting of the Harvey Cushing Society. The abstract discussed the author's comparison of Pantopque to Lipidol.

February 15, 1944 Lafayette Pharmacal Inc.'s, Mr.W.S. Bucke, President, sent the following firm reply letter to Dr. Van Winkle's January 21, 1944 FDA letter requesting additional data regarding Pantopaque.

> In reply to your letter of January 21, we are pleased to enclose here with what we believe to answer all of the questions.
>
> Additional to the data regarding controls and toxicity, we also submit a draft of a proposed revised circular and labels.
>
> The raw material tests are to be conducted in the School of Medicine and Chemistry, in the University of Rochester, both before and after packaging, then arrangements entered into with Eastman Kodak Company and Lafayette Pharmacal Inc.
>
> With this additional data, we trust that the Department will be in a position to act upon our application so that Pantopaque may be available to the civilian population.

Dr. Van Winkle also received a February 16, 1944 letter sent from the Army Service Forces, Seventh Service Command, Neurosurgical Section, O'Reilly General Hospital, Major Francis Murphy, Chief Neurosurgical Section. Dr. Murphy provided the Agency with his experiences using Pantopaque compared to Lipidol:

> At the request of Lt. Col. R. Glen Spurling of Walter Reed General Hospital and Dr. William H. Strain of the School of Medicine, University of Rochester, Rochester, NY, I am writing you concerning my experience with Pantopaque.
>
> ....It is my belief that this substance is considerably less toxic than Lipidol although we have not done spinal fluid examinations following the myelograms for the determination of the cell count in the spinal fluid. There can be no doubt that it is

much more easily removed than Lipidol. The average residual amount in one series was one-tenth of 1 cc when 3 cc's of Pantopaque was used.

Generally speaking it may be said that Pantopaque is clinically less toxic and less irritating than Lipidol and that it is much more easily removed from the spinal subarachnoid space than Lipidol. It is our considered opinion that Pantopaque should be approved by the Food and Drug Administration for use in civilian life.

Dr. Van Winkle received a February 24, 1944 letter from Major Robert Robertson, Chief of Neurosurgery, Brooke General Hospital, Fort Sam Houston, Texas supplying FDA with his personal experience with use of Pantopaque:

Dr. William H. Strain, University of Rochester, School of Medicine and Dentistry, has requested that a report be made to the Food and Drug Administration, New Drug Section, regarding our experience in the use of Pantopaque.

Approximately 250 pantopaque myelograms have been done in the Neurosurgical Section, Brooke General Hospital. 220 of this series have been recently reviewed in detail.....

1. It is easily injected. Usually it is readily recovered, almost, if not completely, through an 18 gauge lumbar needle....As much a .7 to .8 cc out of 1 cc have been demonstrated to be absorbed in the space of one month to 6 weeks. It is hoped that some accurate figure will be determined in further review of these films.

2. Reactions of neural tissue and/or meninges have been rare to minimal. In several cases there has been some *transient nuchal rigidity* of 2 to 4 days duration. Nine cases, due to marked position changes, are known to have had the material enter the cranial cavity....Of these nine known cases, one, an airplane pilot, developed moderate headache which occurred after flying a few days following the Pantopaque study....The other eight cases had no symptoms.

In one case in this series who had a Pantopaque study and operation for a herniated nucleus pulposus, there developed an **adhesive arachnoiditis** (* bold added for emphasis) in the lumbar region, the cause for which was undetermined. It is our opinion that Pantopaque was not the primary cause of this reaction but it cannot be definitely shown.

3. The material shows good opacity and interpretations of the films are as simple as that done with other opaque media.

March 24, 1944, Mr. Fuess of Eastman Kodak Company, Chemical Sales Staff, wrote to Mr. Bucke of Lafayette Pharmacal Inc, regarding Kodak's opinions for the proposed revisions of the Pantopaque labeling. Lafayette Pharmacal had been revising the labeling at the request of FDA to meet the Agency's recommendations. Eastman Kodak continued to hold the Pantopaque

trademark and Lafayette Pharmacal was legally required to obtain Kodak's prior approval of Pantopaque product labeling:

> I am returning the copies of the labels for Pantopaque which you forwarded to use for approval in accordance with our agreement.
>
> As pointed out in my previous letter, the chemical name is incorrectly spelled in both places where it appears. As noted on the copy an "l" should be inserted between the "y" and the "u". Our Patent Department has approved these labels with this change.
>
> We also forwarded the labels to the University for their approval. Dr. Ramsey makes the following statement:
>
> > "In general I feel that the labels are satisfactory but I dislike the inclusiong(sic) of the phrase "After Myelography, remove as much as possible" as part of the label. This gives undue emphasis to the removal, an emphasis that I do not believe is necessary beyond other points in the technique."
>
> Dr. Strain repeats this with a further comment as follows:
>
> > "The labels are satisfactory in every respect except for the typographical errors that you noted, and the inclusion of the phrase "After Myelography, remove as much as possible.: I feel that the letter should not be on the label. In any event "Myelography" should not be capitalized."
>
> My comment on these statements is that my interpretation of the statements from the Food and Drug Administration is that they feel that the inclusion of the phrase in question is essential.
>
> Upon correction of the typographical errors we approve the labels as submitted.

April 14, 1944 Pantopaque's NDA application was approved for marketing in the U.S. by FDA for the intended use for myelography. The product approval appears to have have occurred without resolution of Dr. Van Winkle's concerns regarding the "safety" of the product.

April- July , 1944, Dr. Strain's periodic report on **Radiopaque Compounds** began:

> Pantopaque: The several x-ray houses are offering Pantopaque for sale to physicians in civilian life. To coordinate with the sales effort, an exhibit on Pantopaque myelography has been prepared and a number of papers on Pantopaque Myelography have been submitted for publication.....
>
> During the period April-July, 1944, the final phase of marketing Pantopaque was completed. Assays were conducted for Lafayette Pharmacal, both in April and June,

and the product was announced in June at the annual meeting of the **American Medical Association** in Chicago.

The problem of the policy of the University in marketing new products has received consideration during this period.....

Prior to initiating the final steps for an agreement with Squibb, a discussion was held at the Medical School on the general policy of the University. Those participating in this discussion were : Dr. Whipple, **Col. Warren**,(* bold added for emphasis), Mr. Thompson, Mr. Kappelman, Dr. Strain. The issue was whether the University should send out material for corroborative clinical testing. The argument in favor of such a policy was presented by Strain, who reasoned that the corroborative testing was the most important part of the development of any new product and that it is desirable to keep this in the hands of the University. The other four members of the group felt that the risks of **potential liability** (* bold added for emphasis) of this policy were so great that it could not be considered nevertheless they agreed that any new products should be tested within the Medical School of the University of Rochester. Since this conference, arrangements have progressed further with Squibb so it is probable that an agreement will be made to submit Pantopaque emulsion to clinical trial through this organization.

On May 9, 1944, U.S. Patent 2,348,231, covering Pantopaque and Gavitrast was issued to Strain, Plati and Warren.(* Bold added for emphasis)

July-October, 1944 **Radiopaque Group Compound Report** of Dr. Strain indicted that the exploitation of the civilian market for use of Pantopaque was well under way. An agreement in early August had been concluded with E.R. Squibb & Son for them to study the "**emulsion**" formulation of Pantopaque, but no progress had been made at that time due to the lack of suitable equipment. An initial 8000 ampules of Pantopaque for civilian use had been sold during the period July 1- August 18, with backorder of 4000 ampules.

As other applications of the medium develop the business will increase. The initial skepticism of the x-ray houses on the size of the market have now changed to optimism.

October 1944 , Surgery , authored by Lt. Col. Spurling and Cpt. George Wyatt, **Pantopaque, Notes on Absorption following Myelography,** described intrathecal injection of a Pantopaque dose of 3.5 ccs, began:

Pantopaque has replaced Lipidol and the gases as the contrast medium for myelography in the Army Medical Corps. The chief reason for the preference to lipidol is that Pantopaque is **absorbed** (* bold added for emphasis) instead of remaining as a persistent foreign substance in the subarachnoid space. Experience has shown it to be nontoxic and no more irritating than lipidol, and its sharp radiographic contrast and consequent clear delineation of pathologic anatomy affords

> a definite superiority over the gases as does lipidol. In contrast to lipidol, pantopaque is more fluid than viscous and therefore fills out the smaller spaces such as dural nerve sheaths. **It also is more easily removed following examination.**(* bold added for emphasis)

November 12, 1945, Lafayette Pharmacal, Inc. sent a coverletter to Dr. Merrick of FDA requesting to amended the batch specifications for Pantopaque in their NDA 5-319. In the original provisional specifications for Pantopaque and ethyl iodophenylundecylate, the manufacturing control of the quality of the product had been verified by measurement of physical constants, chemical analyses, and an intrathecal biological assay using injection of dogs. All these controls for manufacturing had been at the recommendations given to Lafayette Pharmacal from Dr. William H. Strain and his associates in Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York, who had been responsible for the development and production of the product. Lafayette's letter to the NDA contained the following new information:

> We have been advised by Dr. Strain that in his opinion, the intrathecal assay in dogs is meaningless "procedure" and does not give critical information for the control of the quality of the product.. Accordingly, in submitting the amended specifications, the **intrathecal assay has been eliminated**,(* bold added for emphasis), and, to compensate for this, the range of each physical and chemical constant has been narrowed.
>
> We understand from Dr. Strain that the proposed changes have been discussed with Dr. Walton Van Winkle, Jr., of your staff.....

April-October 1946 **Report on Radiopaque Compounds** by Dr. Strain, under his discussion of Pantopaque, Dr. Strain indicated that "they" were still working through Lafayette Pharmacal, with some progress made in promotion of clinical indications for Pantopaque **beyond myelography**.(* Bold added for emphasis.). A number of clinical investigators had been supplied with Pantopaque by Lafayette Pharmacal to conduct their own clinical investigations of indications other than myelography. For example, studies were underway at the University of Pennsylvania for injecting Pantopaque into facial sinuses for radiological visualization, as well as utero-tubography, and nerve delineation. Pantopaque was also being investigated for utero-tubography imaging at University of California Hospital, and Michael Reese Hospital in Chicago.

Dr. Strain also wrote regarding the new formulation "**Emulsion**" of Ethyl Iodophenylundecylate

> Through correspondence with a number of surgeons and radiologists it was possible to arouse interest in the **emulsion** (* bold added for emphasis) of ethyl iodophenylundecylate in some six centers. The logical application of the medium appears to be ***bronchoscopy***, (* bold added for emphasis) and, because of this, the program for the study of the emulsion overlaps that for the study of *new fields for Pantopaque*. With either there is a problem of developing new techniques for the

> visualization of the bronchial passages, and currently conditions are not too favorable for such studies; most of the centers of thoracic surgery are in a state of flux as a result of the return of veterans.....
>
> The most progressive results have been obtained at the University of Cincinnati School of Medicine where Dr. Francis McGrath has had a very satisfactory results in the visualization of empyema cavities, and some progress in applying the medium to bronchoscopy. As a result of correspondence and discussion with Dr. McGrath the technique of the bronchogram in dogs has been revised carefully, and a procedure using a 90% emulsion worked out. The results obtained with the more concentrated and more viscous medium are uniformly good.
>
> Applications of the emulsion other than to problems of thoracic surgery have not been as favorable. In ***uretero-tubography*** (* bold added for emphasis) there seems to be a high incidence of transient low-grade discomfort, and in the visualization of the renal bladder there does not seem to be much interest.

During the early part of June, Dr. Strain had a visit to the Montreal Neurological Institute to discuss a **number of "problems" that had occurred relating to their utilization of Pantopaque**. Later in June, he made a trip to E.R. Squibb & Sons to discuss the possibility of transferring the Radiopaque Project to their Institute of Medical Research. From abroad, Dr. Strain had learned that Pantopaque was being manufactured in England by Glaxo and sold under the name "**Myodil**". As a counter measure to this, a Swedish physician delegation studying medical education in the U.S. had been furnished by him with a moderate supply of US produced Pantopaque to distribute when back in Sweden.

December 21, 1950, an untitled memo(?) was issued by Kodak's Color Control Department regarding control of the manufacturing of Pantopaque (000190):

> ***Because of complaints on certain lots of pantopaque***,(*bold and italics emphasis added), it was decided that a more thorough investigation of the compound should be made, aided by the infared spectrophotometer, to see if the cause of the trouble can be found. The "trouble" with the pantopaque was identified to be the presence of **5% iodophenylundecanoic acid rather than 0.9%** (* bold emphasis added). A method was then developed using titration with alcoholic potassium hydroxide to determine the percent of iodophenylundecanoic acid.

In terms of the active "off-label" conductance of clinical research for a new emulsion formulation by Lafayette Pharmacal, March 20, 1950 G.C. Mees, Vice President, Distillation Products Industries, a Kodak Company, wrote to W.S. Bucke, President, Lafayette Pharmacal, the following regarding their business relationship:

> We are writing to confirm the understanding reached at our recent meeting with respect to an arrangement for conducting further work in the preparation and testing of emulsions of Ethyl Iodophenylundecylate in the drug and pharmaceutical field.

As you know, some work along this line has been done under previous arrangements with the University of Rochester and with E.R. Squibb and Sons **but these arrangements are no longer active.** (* bold added for emphasis) We are both desirous that such work shall not be dropped but rather shall be continued on the following basis.

We will supply to you information available to us pertaining to this problem and which shall have been supplied to us by the University of Rochester and E.R. Squibb and Sons under the previous arrangements hereinabove mentioned.

We will furnish to you, on a no-charge basis, such amounts (not to exceed a total of 25 kilon) of Ethyl Iodophenylundecylate as you shall require for carrying on the work contemplated by this letter.

You will prepare emulsions of such Ethyl Iodophenylundecylate in any way you may see fit and supply such emulsions to one of your experts qualified by scientific training and experience to investigate their safety as drugs and you will arrange with such experts to conduct clinical work necessary to establish whether or not such emulsions are suitable for use, and useful, as drugs, all in accordance with the pertinent provisions of the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder.

In the event such work shows satisfactory results, you will prepare a "New Drug Application", or other appropriate application, for submission to the Federal Food and Drug Administration in accordance with the New Drug provisions of the Federal Food, Drug, and Cosmetic Act and seek, by proper means, to secure the approval of such application.

We are advised by you that a "New Drug Application" has been submitted with reference to Ethyl Iodophenylundecylate as such, and that this New Drug Application has become effective, but that another "New Drug Application", or perhaps an amendment to the earlier application, may be required in connection with the emulsions of Ethyl Iodophenylundecylate which you will prepare. You accordingly agree that such emulsions will not be introduced or delivered for introduction into commerce by you except in accordance with the pertinent provisions of the Federal, Food, Drug and Cosmetic Act relating to new drugs, to wit, Section 505 and the regulation promulgated thereunder.

It is further understood and agreed that our company assumes no responsibility whatsoever with respect to this arrangement except to supply you with the above-indicated amounts of Ethyl Iodophenylundecylate.

You agree that the "Ethyl Iodophenylundecylate" will be referred to and described only by that name and that no trade-mark of our company will be used in any way in connection with your activities under the arrangement, except with the express

written consent of our company.

This letter serves to document that the University of Rochester, School of Medicine and Dentistry and Dr. Strain were no longer actively involved with the manufacturing, investigation and promotion of Pantopaque in the U.S.. Significantly, the change in testing site was a potential significant "alteration" in the batch release criteria that had been specified within the NDA for manufacturing product control and quality oversight. Such a change could potentially have been viewed by FDA, if they were not informed, as having a potential impact on the "safety" of the product sold by Lafayette Pharmacal, Inc. and approved for marketing under NDA#5-319. Also, Lafayette Pharmacal and Kodak's Distillation Products Industries (DPI) demonstrated in the letter that they had an awareness of need to appear to meet the requirements of the FDCA for conducting clinical research as well as the need to obtain clearance from FDA for the legal marketing of the Ethyl Iodophenylundecylate emulsion formulation.

In the 1950 letter, Mr. Mees of Kodak's Distillation Products Industries attempted to assign all responsibility for compliance, manufacturing and fulfillment of FDCA's requirements onto Lafayette Pharmacal. The intent of Kodak's letter appeared to create "legal distance"for Kodak and Kodak's Distillation Products Industries from any potentially illegal ramifications for actions that may result from Lafayette's distribution of the emulsion formulation within the U.S. However, Mr. Mees also indicated that his firm wished to take steps to facilitate future marketing, investigation and development of the product.

1953 Lafayette Pharmacal Inc.'s Pantopaque labeling as it appeared in The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, December 3, 1953, indicated a usual Pantopaque myelographic study employed injection of **6 or 9 cc** of contrast media.

(* The 1944 draft labeling and all information provided to FDA in the NDA for Pantopaque recommended a myelography dose of **"2-5" cc.**)

Lafayette Pharmacal's labeling continued to make no reference to potential serious acute or long-term consequences associated with intrathecal injection of Pantopaque which had been the expressed concern of FDA's reviewer, Dr. Van Winkle, for injection of a dose of **2-5 cc**, nor did the labeling appear to emphasize the need to remove all the material following imaging. The labeling emphasized injecting a larger dose of Pantopaque for imaging of the spinal column then had been provided to FDA in NDA 5-319 (i.e. 2-5 cc) with the availability of "multiple size" ampules.
The labeling stated:

The contrast medium of choice now available in 3 sizes.
(3 cc, 6cc, 12cc).

(*Note: In terms of the favorable reported clinical experience in the military imaging populations, Major Spurling's study that appeared in Surgery October 1944 had indicated an injected Pantopaque dose of **3.5 cc**; Major Murphy reported positive results with an injected dose of **1-3 cc** of Pantopaque.)

The labeling also had the following information regarding product utility:

> ***Dynamic Myelography***
>
> *These two radiographs of the same patient demonstrate the bulging of the annulus fibrosous during hyperextension and flexion, respectively, of the vertebral column.* ***30 cc*** *of Pantopaque contrast medium was used. Note how this technique permits visualization of the posterior surface of the vertebral canal.*
> *"PANTOPAQUE" is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*
> (A-0000352).

C. A New Phase of "Pantopaque" Development

Pantopaque II or IND1-161 and NDA16-377

Strengthening of the drug provisions of the 1938 Act had been the focus of Senate hearings held in June 1960. These hearings chaired by Senator Estes Kefauver of the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary, resulted in S.3815. This bill was aimed to protect the public health by instituting certain manufacturing practices, expanding antibiotic certification to all antibiotics, and by other measures.

During the Kefauver hearings, FDA had received an NDA for marketing of Kevadon, the brand of thalidomide that the William Merrell Company wanted to market in the U.S. Despite ongoing pressure by the firm, medical officer **Frances Kelsey** refused to allow the NDA to become effective because of insufficient safety data. By 1962 thalidomide's horrifying effects on newborns had become known. Even though Kevadon was not approved for marketing, Merrell had been able to distribute over two million tablets for "investigational use", a use which the FDA's regulations and laws had left unchecked. For her efforts, Dr. Kelsey received the President's Distinguished Federal Civilian Service Award in 1962, the highest civilian honor available to a government employee.

As a result of the narrowly avoided tragedy, Senator Kefauver re-introduced his bill. On October 10, President Kennedy signed the Drug Amendments of 1962, also known as the Kefauver-Harris Amendments. These amendments required drug manufacturers to prove to the FDA that their products were both safe and effective prior to marketing. They also gave FDA control over prescription drug advertising. The Drug Amendments addressed the use of drugs in clinical trials, including requirement for informed consent by subjects and obtaining an Investigational New Drug (IND) exemption from FDA. FDA was now required to be provided with full details

of drug clinical investigations, including drug distribution, and IND clinical studies had to be based on previous animal investigations that could assure "safety".

The FDA's National Center For Drug Analysis (NCDA) opened in St Louis, Missouri, in July 1967 began to conduct large scale tests of drug products. Prior to this, NCDA had been part of the Division of Pharmaceutical Sciences in FDA's Bureau of Science. In its first year, the NCDA examined over 7,000 samples. Therefore, FDA, since the approval of NDA5-319, had begun to develop the Agency's evaluation capabilities for examining of the quality of drug products that were to be manufactured and sold in the US.

November 20, 1964 there was an interagency memo from Mr. Hagan, Division of Toxicological Evaluation (DTE) to Medical Officer **Dr. Frances O Kelsy** (* bold added for emphasis), Division of New Drugs (DND) regarding Lafayette Pharmacal Inc.'s **IND 1-161 (Investigational New Drug exemption)** to legally begin to conduct human clinical trials for support of safety and efficacy for Pantopaque II to obtain the Agency's approval for marketing of a 15% (iodine content) Pantopaque (Pantopaque II). There was an Agency memo that suggested Lafayette Pharmacal had begun interacting with FDA prior to November 1964 to obtain future approval of "Pantopaque II". The changes in the FDCA had greatly modified the route for Pantopaque II to reach the U.S. market when compared to the World War II 1944-era "Pantopaque I" approval based only on "safety" and culled reports of positive physician experience with military patients.

Mr. Hagan of FDA's DTE characterized that each 20 ml of Pantopaque II product submitted to FDA for the IND contained "10 ml Iophendylate and 10 ml Ethylphenylundecanoate", as an absorbable iodinized fatty acid compound of low viscosity intended for myelography. Lafayette Pharmacal was now requesting to substitute a material yielding a "15% iodine" content for the current "30% iodine" content Pantopaque I material. FDA's reviewers were referred by Lafayette Pharmacal back to the original NDA to review animal toxicity data submitted for the Agency's approval of "safety" of Pantopaque in NDA 5-319.

Mr Hagan as part of the Agency's toxicological evaluation reviewed the animal toxicity data for Pantopaque submitted in Lafayette Pharmacal's NDA 5-319. He wrote of his major concerns regarding the production of " **fever"** induced by injection during animal studies and how the fever appeared to be related to the **pyrogenicity** of the product. He was also under the impression from sources outside Lafayette Pharmacal that the iophenydylate (30%) intrathecal dosage for myelography was **6-12 cc.** Mr Hagan determined that Pantopaque 30% had produced a significant fever rise during the NDA's when injected into humans during the original clinical studies. To better characterize the deficiencies in Pantopaque's animal toxicity data in the NDA#5-319 and what would now be required in the NDA, he wrote:

> Despite the 20-years history of use of this drug, we should have *acute toxicity* data in perhaps dogs or rabbits in which the 15% material is administered by intrathecal administration. Effort should be made to relate the use levels to that causing death in toxicity studies. Directions contraindicate repeat of dosage within 10 days. We suggest a repeat of *3 times a therapeutic intrathecal dose* in animals after a 10-day

interval. If effects result then a repeat of the foregoing procedure should be made at a lower dosage.

January 26, 1966, attorney Bradshaw Mintener wrote Mr. J. Hauser, FDA, Bureau of Medicine, regarding **IND#1-161** submitted by his client Lafayette Pharmacal. He indicated that Lafayette Pharmacal had previously filed IND#1-161 on June 6, 1963 to market Pantopaque with 15% iodine. He referenced the NDA that had approved Pantopaque (30%) in 1944, the comparison of the new Pantopaque product, and the firm's desire to now withdraw IND1-161 and submit the marketing application as a supplement to NDA5-319:

> In the course of years, because of the ***trend toward using greater volumes*** (* bold and italics added for emphasis) of Pantopaque, and because the great density even within the usual amounts of Pantopaque 30% may obscure the more subtle shades of the spectrum of density which one uses to detect the presence of compressive lesions involving the subarachnoid space, many neurosurgeons and radiologists have requested a less dense material.
>
> Accordingly, the iodination of ethyl phenyl undecanoate was decreased to give a 15% iodinated Pantopaque. This gives a corresponding decrease in specific gravity to 1.09, as compared to 1.25 for the standard 30%.
>
> An IND application-#1161 and dated June 6, 1963 was filed with the Food and Drug Administration covering the 15% product and supplemental information was subsequently submitted to the Department as well as reports of clinical studies.
>
> In view of the fact that the 15% product is the same as the 30%, save for the iodinization producing a product with less iodine content, Lafayette Pharmacal would like to submit this ***supplemental application to their NDA 5319 and recall their IND application 1161, if this is necessary....***(* bold and italics added for emphasis)
>
> Pantopaque is distributed by seven major x-ray companies as well as Lafayette Pharmacal, Inc. and enclosed you will find labeling for all distributors.
>
> The study performed at the Neurological Institute was exhibited in the scientific section of the American Neurological Association Meeting, held June 14-16, 1965 in Atlantic City.

March 17, 1996 Mr. W, S, Bucke, President of Lafayette Pharmacal, Inc. wrote to Dr. Frances O. Kelsey, Chief of Investigational Drug Branch, Division of New Drugs regarding the status of IND 1161:

> Thank you very much for the courtisies extended during my recent visit to your office and this will confirm our discussion relative to your letter of February 17, 1966.

> The **error in the IND number** (* bold added for emphasis) occurred in the office of Mr. Bradshaw Mintener in his letter of January 26, 1966 addressed to Mr. Julius Hauser.
>
> Referring to paragraph #3 of your letter of February 17, 1966, we do not wish to discontinue our study under Exemption (IND 1161), our reason being that on the suggestion of Mr. Julius Hauser, Bureau of Medicine, we have filed a supplemental application. This was filed by us by Mr. Bradshaw Mintener and we are awaiting your opinion on this supplemental application.

FDA did not accept the proposal of Lafayette to submit Pantopaque II as a supplement to NDA 5-319 and withdraw IND 1161 for obtaining clinical data for inclusion in a new NDA. Dr. Kelsey and her staff had determined that FDA's marketing approval of Pantopaque II was to require the submission of a **separate new NDA** to FDA by Lafayette Pharmacal.

FDA's reviewer Elton Herman, MD prepared a **4/29/1966** summary of **NDA 16-377** sponsored by Lafayette Pharmacal, Inc. regarding the approval of Pantopaque II (Iophendylate Injection). The current intrathecal dose recommendation listed was still the **2-5 cc** dose injected into the subarachnoid space of NDA5-319. The general category of the drug was intended as a diagnostic agent for myelography, indicated to be particularly satisfactory for study of the lumbar region. The structural formula was of a mixture of isomeric ethyl esters. Pharmacology information included a report dated January 19, 1962 of a study conducted at **Hazleton Laboratories** regarding acute intraperitoneal injection in 8 rats and acute intramuscular irritation study in 2 rabbits. He concluded:

> DTE review of *11/20/64* requested "*acute toxicity data* in perhaps dogs or rabbits in which the 15% material is administered by intrathecal administration," as well as repeat dosage after 10 days using 3 x the therapeutic dosage; *apparently none of these were ever performed and no further explanation is provided.*
>
> One of the investigators reported under clinical studies performed preliminary dog work with one control dog given 30% Pantopaque intrathecally and two given 15%; amount given is not stated but it was apparently sufficient to perform an adequate myelogram. Baseline CSF studies were done and repeated after 6 weeks (Pantopaque was left in the subarachnoid space during this period), and the dogs were sacrificed and autopsied. Examination of one of the 15% dogs could not be performed as there was "an interval between sacrifice and post-mortem in which major autolysis took place." Both 15% dogs, on the 6-week post-myelographic CSF test, showed " modest protein elevation" and "slight inflammatory response with increase in WBC, similar to the response of the original dog work" utilizing 30%. Histology report on the 30% dog is reported as "O.K. No histologic abnormality" and on the 15% dog as "Histology normal." It is stated that evaluations were "comparable; if anything, the 15% Pantopaque dog showed less inflammatory response in the form of lymphocytic and polymorphonuclear cell infiltration." As the original 30% product is commercially available and the new preparation is less

concentrated than it, "it was felt that no further laboratory work need be done."

VI. Clinical studies:
No case reports are included from any investigator in either the NDA or IND. IND 1161 filed for this product contains statements of investigation and brief protocols for study from 5 investigators or groups, all of whom appear to have good credentials; for 3 of these, there is no follow-up, report, summary, or result of any type given. Of a fourth investigator, it was later said in a letter from the firm that he, "Due to pressing duties,....did not enter into any investigational work."

The fifth group of investigators, Drs. E. Ralph Heinz, Ray A. Brinker, and Juan M. Taveras, from the Neurological Institute, New York (the same group which performed the above-described pharmacologic 3-dog study), have also not submitted any case reports but they have sent in a brief summary of 117 patients studies between 8/1/63 and 5/31/64; of these, approximately half received 15% or 221/2% (equal volumes of 15% and 30%) Pantopaque and were compared to the remainder in whom only 30% was used. The first 20 patients were "checked clinically for signs of meningeal irritation, fever, or other untoward effect following instillation of the lesser concentration, and no abnormality was found. Subsequently, additional patients have been added without any detectable objective or subjective abnormality...." The authors conclude that they "have been better able to visualize the spinal cord utilizing the less concentrated contrast, as well as visualize small differences in density when external compression of the subarachnoid space is present. The authors feel that this less concentrated Pantopaque offers definite advantages over the conventional 30% Pantopaque. However, they offer no objective confirmation of these claims, no individual case reports, and no criteria by which they measure "better" visualization or "small differences" in density.

VII. Labeling:
Discussion seems completely superfluous at this point, except to state that , save for omission of a section describing "Technique for Large Volume Dynamic Myelography" and the obvious changes in the portion dealing with chemical and physical characteristics so as to describe the 15% preparation, the labeling exactly reproduces that last approved in 1960 for 30% Pantopaque.

VIII Conclusions:
The application is <u>incomplete</u> (* underlining added for emphasis) under section 505(b)(1), in regard to clinical studies, because of failure to report in full investigations that have been made to show whether or not the drug is safe for use and effective in use, failure to include adequate case reports concerning each subject given the drug or employed as a control, and failure to include substantial evidence consisting of adequate and well-controlled investigations.

Final comment on labeling will be reserved until the application is complete in its other respects.

At the bottom of the reviewer's report there is also a handwritten note from A. Ruskin dated 5/4/66:

> Should pharmacologic work be complete before any further human tests? Is there an IND?

Reviewer E. Herman wrote a reply dated 5/5:

> There is an IND with reports as stated above.

There was then an FDA Intra-Administrative Referral issued 5/5/66 to Investigational Drug Branch (IDB), Division of Toxicological Evaluation (DTE) from E. Herman, MD of the Medical Evaluation Branch:

> This NDA will be incomplete by letters that should issue within several weeks. In accordance with question raised by Dr. Ruskin, do you feel pharmacologic work should be completed before any further human tests?

DTE's response:

> DTE review of 11/20/64 did request "acute toxicity data in perhaps dogs or rabbits," *but apparently never performed.*

A.R. Casola, Ph.D., FDA's Manufacturing Control Branch (MCB) authored a June 15, 1966 draft of controls portion of letter intended for Lafayette Pharmacal regarding NDA 16-377. The reviewer determined that the application was "incomplete". The NDA failed, among many other things, to provide adequate information regarding the qualifications, educational background and experience of the technical and professional personnel responsible for assuring that the drug had the safety, quality and purity it purported. The applicant was also requested to submit information regarding the facilities and personnel for Taylor Pharmacal Co., **Distillation Products Industries** and for Analytical Chemists. The applicant had not submitted to FDA the required samples for agency evaluation and had not submitted the draft labeling required for all distributors.

October 3, 1966, FDA's reviewer James E.Wilson, Ph.D., wrote the agency's pharmacological review that also found the NDA incomplete pharmacologically. The new drug name was Pantopaque II and the recommended injection dose for myelography was "**2-5 cc**". The following was his evaluation of the NDA:

> Pantopaque II is a 1:1 (v/v) mixture of iophenylate (Pantopaque) and ethyl phenylundecanote. Iophenylate has been on the market for twenty years but deaths have been attributed to its use. Recently, Swartz (New England J. Med. 272, 898-902, 1965) cites a case report of a 61 year old woman who died of **obliterative arachnoiditis** (*bold added for emphasis) with hydrocephalus one year after cervical myelography using iophenylate. Whether the response was a direct result of

chemical irritation or a form of hypersensitivity could not be ascertained.

In its review (11/20/64) of IND 1161, Pantopaque 15%, DTE recommended that acute toxicity tests be performed in either the rabbit or dog using single administration of iophenylate or the 1:1 mixture have been performed by workers at the Neurological Institute (New York). These investigators examined the cerebrospinal fluid and histologic sections of the cerebrospinal axis. The test however, needs repeating since the dosage level (approximated at 0.1 ml. or gm/kg) was within the human therapeutic range (**2-5 ml**)(*bold added for emphasis) and did not approach toxicity or lethality. Further, the number of animals used (only 2 autopsies) was too small for a valid evaluation.

Some attention should be devoted by the applicant to the development of a hypersensitivity towards the drug. A suggested test is the intrathecal administration of the drug to dogs with a subsequent challenge 2-3 weeks later.

The application is considered incomplete.

October 21, 1964, from a memo to the NDA record by W. Gyarfas, MD, Mr. Mintener, without an appointment, visited the FDA offices to inquire about the status of NDA 16-377 and to resubmit information from the Neurological Toxicity Studies (*information that had been previously submitted by Lafayette within both the IND and the NDA). He also inquired of Dr. Gyarfas what would be required for Lafayette to answer the agency's letter of October 11, 1966 that had again requested the submission of an over-due progress report of the status of the clinical studies.

The *inadequacies of the NDA* were reviewed with Mr. Mintener, who seemed unprepared to discuss the issues, and Mr. Mintener kept making references to "Julius" and "old timers". Mr. Mintener indicted that he would inform his client Lafayette Pharmacal how to bring their IND up-to-date and recommend that they complete their NDA.

May 4, 1967, Dr. Gyarfas again recorded that he was visited, but this time by Mr. Bucke of Lafayette, who also visited the FDA offices without an appointment to ask questions regarding the application. Mr Bucke inquired about the ability to use foreign clinical investigators. He was informed that foreign investigators would also be required to sign FD Form 1573 and that their data would also be carefully evaluated by FDA.

Safety Animal Studies for Pantopaque I and II

September 7, 1967, Hazelton Laboratories completed an *Acute Intrathecal Toxicity Study-Rabbits* involving 16 rabbits using Pantopaque II that were followed for 14 days. The study data was submitted to Lafayette Pharmacal, Inc. The summary of the study went as followed:

Pantopaque II was evaluated for acute intrathecal toxicity by intraspinal injection to

groups of adult albino rabbits (* 4 groups of 4 rabbits each) at graded dosage levels ranging from 0.562 to 316 g/kg of body weight. Partial mortality at the two lower levels and total mortality at the two higher levels were produced. The mortality pattern did not permit an accurate calculation of the acute intrathecal LD50, but it is estimated to be in the order of 0.5 g/kg of body weight.

Principal Toxic Effects Observations noted during the 14-day period consisted of the following: Slight ataxia at the four-hour observation period only in all animals at the lowest level and in two animals at the 1.0 g/kg level, rapid respiration prior to death in one animal at the 1.78 g/kg level, limited use of the hindquarters in two animals, and terminal body weight loss in all animals at the lowest level; partial mortality at the two lower levels and total mortality at the two higher levels.

November 13, 1967 Hazelton Laboratories submitted *Acute Intrathecal Toxicity*- Dogs Pantopaque II to Lafayette Pharmacal, Inc. The investigation had been conducted from July 27, 1967 through September 6, 1967. The summary of the data was as follows:

Single intraspinal doses of the test material, Pantopaque II, were administered to four groups of two dogs each, at levels of 0.316, 0.562, 1.00, and 1.78 g/kg, respectively. The dogs were observed for 14 to 20 days after dosing and then sacrificed.

All dogs showed signs of muscular weakness and incoordination following dose administration, with particular loss of motor control of the hindlimbs. The degree of this motor incoordination did not appear to be related to the dose level.(* underlinging added for emphasis) All animals slowly returned to normal or near normal appearance during the observation period except one low level animal which died after two days, apparently from an injury sustained during injection of the compound.

Gross necropsies after sacrifice revealed the presence of oily substance resembling the test material in the cerebro-spinal fluid of all but two animals. Connective tissue lesions in the area of the injection were present in about half the animals.

The dog that died had received the **lowest dose** Pantopaque II dose, Group No. 1, (0.316 g/kg) and had appeared normal on the day of dosing. (*Two dogs were used in each of the 4 dose groups.) On day 2, its behavior became vicious and it was found dead on day 3. The other animal in the low dose group appeared normal for several days following dosing. However, on the day 4, the animal appeared uncoordinated and became partially paralyzed in the hindlimbs. The dog's condition returned to normal by day 8, but it continued to lose weight throughout the study until termination.

For the two dogs in the next dose group, Group No. 2, (0.562 g/kg), both became markedly uncoordinated with partial paralysis in the hindlimbs. Their conditions gradually improved until sacrifice.

Group No. 3 dogs (1.00g/kg) both exhibited signs of muscular weakness and poor coordination following dosing. Partial paralysis of the hindlimbs were apparent in both and improved in one animal. A similar picture occurred in the highest dose group, Group No. 4, (1.78 g/kg), with initial muscular weakness, lack of coordination and slow improvement until time of sacrifice.

Histologically, all animals in Groups No. 2 and 3 had connective tissue lesions of varying severity found at the location of injection. The dog in Group No. 1, the lowest dose group, that died had hemorrhagic and purulent-appearing areas at the base of the medulla and between the meninges and the spinal cord. The spleen of this animal was enlarged to twice normal size. For all dogs, at autopsy, traces of oily substance, varying in amount approximately proportional to the administered dose level, were found within the cerebrospinal fluid.

Almost two years later, *February 7, 1969*, Hazelton Laboratories completed the study *15-Week Intrathecal Toxicity Study*- Dogs which was a comparison of Pantopaque I and Pantopaque II. The data was submitted to **Kodak's *Distillation Products Industries***, Rochester, NY, not to Lafayette Pharmacal, Inc as had been done with the earlier studies. The purpose of the study was to evaluate the long-term effects of Pantopaque II when compared to Pantopaque I after being left within the spinal column of dogs. Pantopaque I was a lot that had been received by Hazelton Laboratories from Lafayette Pharmacal on November 27, 1967, Lot No. 129666, and appears that it may have been a production lot. The purity was "assumed" to be 100%.

Pantopaque II was identified as ethyl phenylundecyclate combined with 15% organically bound iodine (Lots No 91347 and No. 91374), and appears that it was an experimental product. It was received July 24, 1967 and November 27, 1967 from Lafayette Pharmacal. The purity also was "assumed" to be 100%.

The study used 24 purebred Walker hounds, divided into 2 dosage groups (0.014 ml/kg) or (0.14 ml/kg) of either Pantopaque I or II compounds, for a total of 4 groups. The test material was administered by a single injection into the cisterna magna, with all dogs observed for 15 weeks. Full spine lateral x-rays were made for each dog following injection and at regular intervals of 30 and 60 minutes, 3, 24, and 48 hours, and one to two weeks thereafter. Only the brain and spinal cord were examined microscopically.

Five animals that received Pantopaque II at 0.14 ml/kg showed a marked increase in leukocyte counts at 24 hours. Five dogs had clotted blood present at the base of the brain and anterior spinal cord - one Pantopaque I and four Pantopaque II. Eight dogs had meninges visibly thickened- three Pantopaque I and five Pantopaque II. In two dogs, both Pantopaque II dogs at 0.14 ml/kg, there were adhesions to the floor of the vertebral column. In 6 dogs, oily material was grossly seen in the meninges- three Pantopaque I and three Pantopaque II.

Two Pantopaque I dogs receiving 0.014 ml/kg (No. 12686) (No. 12705) (* the lowest dose) microscopically at autopsy had moderate to severe granulomatous reaction surrounding large vacuoles in the space under the meninges and surrounding some of the spinal nerves. The granulomatous reaction involved spinal nerves. There was moderate to severe fibrosis surrounding the spinal cord and scattered areas of granulomatous reaction were present within the

white matter of the spinal cord. Most of the granulomatous reaction was associated around large, clear empty (cystic) vacuoles. The spinal cord was surrounded by moderate amounts of old blood present under the meninges. A Pantopaque I dog that had received the same dose (No.12694) had a similar microscopic picture of granulomatous reaction and fibrosis with cystic spaces but had a moderate amount of fresh hemorrhage under the meninges.

Pantopaque II dogs receiving the lower dose level (0.014 ml/kg) appeared to have gross acute bleeding at all levels of the spinal cord and brain. Microscopically there was perivascular infiltration of meningeal vessels and spinal cord involving macrophages and mononuclear cells, and scattered clear cystic spaces.

Pantopaque II dogs at the higher dose level (0.14 ml/kg) appeared to induce a greater active inflammatory response component. The granulomatous inflammatory reaction was moderate to severe infiltration of mononuclear cells, macrophages, lymphocytes surrounding clear cyst-like areas, moderate to severe adhesion of the arachnoid and dura mater to the spinal cord. Histologically, sections of the spinal cords resembled areas of severe granulomatous reaction seen with Pantopaque I. Severe granulomatous infiltration extended down to the cauda equina, with moderate thickening of the arachnoid, and areas of compression of the spinal cord.

The following was the summary of Hazelton Laboratories, William M. Busey, DVM, Ph.D.'s findings:

> The intrathecal administration of Pantopaque I and Pantopaque II to mature Walker hounds produced varying degrees of granulomatous meningitis in the brain and spinal cord. In the majority of instances, in the animals possessing meningitis, the inflammatory reaction appeared to be associated with empty vacuoles which could possibly have been the experimental compounds. In addition to the granulomatous type of cellular infiltration, there were varying degrees of fibrosis and thickening of the meninges of the both the spinal cord and brain.
>
> In the group receiving Pantopaque I, at a dosage level of 0.014 ml/kg, subdural granulomatous inflammation was present to a moderate to severe degree in three animals.....
>
> Only a slight to moderate amount of granulomatous inflammation was seen in three of the animals receiving Pantopaque II at 0.014 ml/kg. A slight amount of granulomatous inflammation was present in the cervical and thoracic regions of the spinal cord in Animal No. 12700. There was, however, in this animal, a moderate degree of meningitis in the brain which was associated primarily with two vacuoles in the region of the medulla oblongata.....
>
> There did not appear to be any difference in the incidence or severity of granulomatous meningitis between the animals receiving Pantopaque I at 0.14 ml/kg and those receiving Pantopaque II at 0.14 ml/kg. Severe granulomatous meningitis was seen in the cervical regions of all of the animals in these two test groups. In

addition to the inflammatory cellular infiltration, there was severe fibrosis in this region of the dura mater and arachnoid. .....

The majority of the animals receiving Pantopaque I and Pantopaque II at 0.14 ml/kg also possessed some degree of meningitis of the brain.....

In conclusion, it can be stated that the intrathecal administration of Pantopaque I and Pantopaque II at 0.014 ml/kg and 0.14 ml/kg stimulates a ***granulomatous meningitis*** (*bold and italics added for emphasis) in the areas where the compounds appear to localize. The majority of the inflammatory reactions present in the animals on this study were of a subacute to chronic nature. There was a definite difference in the location and severity of the inflammatory reaction between the two dose levels. The dosage level of 0.014 ml/kg of Pantopaque I stimulated a granulomatous reaction in primarily the lumbar region; whereas, the dosage level of 0.14 ml/kg of both Pantopaque I and Pantopaque II produced severe reaction in the cervical and thoracic cords. Granulomatous inflammation was also present in the lumbar cord but to a slightly less degree of severity and incidence.

February 10, 1969, Hazelton Laboratories submitted the final report of the Teratology Study with Rabbits and Pantopaque II to Distillation Products, Rochester, NY. The purpose of the study had been to evaluate the potential of Pantopaque II to produce *embryotoxic and/or teratogenic* effects in a study population of albino rabbits. Peanut oil was administered as a control injection to Group No. 1, Pantopaque I to Group No. 2, and Pantopaque II to Group No. 3 rabbits. Each experimental group, which consisted of 40 rabbits, was divided into four subgroups of 10 animals each. The first subgroups received a single dose of the appropriate injection two days prior to insemination; the second subgroups received a single dose of the appropriate injection on Day 5 of gestation; and the third and fourth subgroups were injected on Day 8 and Day 11 of gestation, respectively. The study was begun on June 25, 1968, with sacrifice of the last groups of females completed on September 6, 1968.

The final results indicated that there were no meaningful differences between the peanut oil, Pantopaque I and Pantopaque II groups in the number and placement of implantation sites and live fetuses, in the weights and lengths of the fetuses, or in the incubation survival. Females with implantation sites unaccounted for were found in the peanut oil and Pantopaque I groups. The number of resorption sites and incidence of **females with resorption sites were high in both the Pantopaque I and II females. The mean value of dead fetuses in the <u>Pantopaque I group was high</u>**; (* bold added for emphasis) however, one female only was found with dead fetuses, and the value for this parameter was within normal limits. No dead fetuses were found in the Pantopaque II group.

No unusual findings were noted in the external appearance or gross visceral anatomy of any of the fetuses. The development and skeletal structure of the Pantopaque I and Pantopaque II fetuses were comparable to that the peanut oil (control) fetuses. Therefore, the response for Pantopaque II was essentially the same as for Pantopaque

I.

April 14, 1969, FDA's Associate Director for Marketed Drugs, Marvin Seife, MD issued Lafayette Pharmacal, Inc. a letter regarding the status of NDA 5-319.

> Our records indicate that you have not submitted any annual reports as required by the provisions of regulations 130.13 and section 505(j) of the Federal Food, Drug and Cosmetic Act.
>
> The failure to maintain the required records and make the reports pursuant to the authority under section 505(j) of the Act may result in withdrawal of the approval of the new drug application, and is prohibited.
>
> In addition for the sake of uniformity and the convenience of the physician, it is recommended that the labeling of your product and those of your distributors, be revised to contain sections in the following order:
>
> NAME OF THE DRUG
> DESCRIPTION
> ACTIONS
> INDICATIONS
> CONTRAINDICATIONS
> WARNINGS
> PRECAUTIONS
> ADVERSE REACTIONS
> DOSAGE AND ADMINISTRATION
> OVERDOSAGE
> HOW SUPPLIED
> REFERENCES
>
> Further we recommend the following:
>
> 1. Delete the statement "The small amount of material left in the subarachnoid space is usually absorbed in two months."
>
> 2. In the INDICATIONS section state the substance of the following: "Pantopaque is indicated for the performance of myelography."
>
> 3. In the ADVERSE REACTIONS section include the following:
> a. Severe arachnoiditis producing headache, fever, meningismus, pain in the back and extremities and elevations in the white blood count and the protein count of the cerebrospinal fluid.
>
> b. The incidence and severity of arachnoiditis are generally increased when active subarachnoid bleeding has been induced by the lumbar

puncture.

c. Rare instances of the development of lipoid granulomas, obstruction of the ventricular system and venous intravasation producing pulmonary emboli.

4. In the CONTRAINDICATIONS section include the substance of the following:

"The administration of Pantopaque is contraindicated in patients with known hypersensitivity to iodine or its compounds. Intrathecal administration should be deferred if bleeding is encountered in the performance of the lumbar puncture."

5. In the PRECAUTIONS section, note that diagnostic tests of thyroid function involving measurements of iodine may be invalidated for several years following intrathecal injection of Pantopaque.

6. In the DOSAGE AND ADMINISTRATION section the amount commonly use as **3 to 12 ml.** (* Bold added for emphasis)

Please submit the reports and let us know your proposal to the above recommendations within ten days of the receipt of this letter.

Lafayette Pharmacal's Withdrawal of NDA 16-377 for Approval of Pantopaque II

June 25, 1969 Lafayette Pharmacal's President W. S. Bucke wrote to Dr. Grigsby of FDA to request to withdraw NDA 16-377 for marketing approval of Pantopaque II. The reason that was given to FDA for withdrawal of the NDA was as followed:

Based on the summaries of the three principal investigators who studied 203 cases (91% of total), it is concluded that Pantopaque II containing 15% organically bound iodine has <u>no real improvement</u> (* underlining added for emphasis) over conventional Pantopaque (Iophendylate Injection, U.S.P.) containing 30% iodine.

Supplies of Pantopaque II sent to clinical investigators have been recalled and inventories have been balanced with the amount shipped and returned. Case reports from investigators have been summarized and are included in Volume III.

The information submitted with this letter has been compiled according to the form described in regulation 130.4(e) and represents the complete data on the subject. It is presented as three volumes, in triplicate.

June 25, 1969, Mr. Bucke also wrote to FDA to withdraw IND #1161 for Pantopaque II. The letter indicated that the case reports of IND 1161 were included in NDA 16-377, and were being

submitted in lieu of the annual progress reports.

June 26, 1969, Memorandum of a Telephone Conversation, was written by F. Grigsby, MD of his discussion with Dr. Kunz of Lafayette Pharmacal, Inc.. Dr. Kunz had called Dr. Grigsby to inform FDA that Lafayette was officially going to withdraw NDA 16-377 for marketing of Pantopaque II (15%). Dr. Kunz indicated that the firm's reason for withdrawal of their Pantopaque II marketing application was that the firm had found that the 15 % Pantopaque was no more effective, and frequently less effective, then the currently marketed 30% preparation.

Dr. Kunz was informed by Dr. Grigsby that if no further clinical studies were contemplated for the 15% Pantopaque II that IND 1161 should also be discontinued by Lafayette's submission of an amendment to the IND with a reference to the clinical studies that have or will be submitted to the NDA before its official withdrawal. The "Notice" reference may serve in lieu of the annual progress report. In addition the amendment to the IND should include information respective to notification to all clinical investigators of their action and to the disposition of the remaining drug.

From the memo, and the letter to FDA to withdraw the IND and NDA for Pantopaque, there appears to have been **no mention** by either Mr. Bucke or Dr. Kunz of the **adverse findings** of the animal safety studies done by Hazelton Laboratories relative to the **equivalent poor safety** performance of both **Pantopaque I, the approved product, and Pantopaque II, the investigational product.** Therefore, FDA was not informed that the animal toxicity studies did not support the "safety" of Pantopaque I.

June 27, 1969, Memo of a Telephone Conversation of another conversation held between Dr. Grigsby and Dr. Kunz, and after the writing of Lafayette's withdrawal letters by Mr. Bucke.

> Dr. Kunz stated that he had collected all data in their possession and that their annual progress report is due within one or two months. He referred to this new drug application as one pending with FDA for approval but they have found the Pentopaque (sic) 30% produces no better visualization than 15% and in fact in some instances it is worse.
>
> He stated that he will be in the District of Columbia within the next few days and will leave an amendment to the IND discontinuing clinical studies. He was told that he may cross reference the information on clinical studies reported in the NDA to serve as a progress report for the IND. He was also advised to state the reasons for discontinuing the study and to inform us as to the final disposition of the drug and notification of all clinical investigators. He thanked me for the information and terminated the conversation.

Technically, the Hazelton Laboratories data had not sent the more damaging conclusions of their animal studies obtained in 1969 directly to Lafayette Pharmacal but rather had sent them to Kodak, Distillation Products Industries Division, Rochester, NY. Therefore, it is "unclear" whether the most unfavorable Hazelton Laboratories animal safety data for both Pantopaque I and II sent to Kodak would have been in Dr. Kunz's "physical possession" at Lafayette

Pharmacal when he spoke with Dr. Grigsby. It is also unclear whether the performance animal data obtained with both "approved" Pantopaque I and "investigational" Pantopaque II were ever shared with FDA within the three volumes of submitted "clinical data" for withdrawal of the NDA.

Dr. Grigsby documented in his memo that he clearly was indicating to Dr. Kunz that the firm was to be **forthright and honest** with the agency regarding providing **all known product** information and **all reasons for withdrawal** of the Pantopaque II marketing application. It would have been assumed that Lafayette management would have known to be honest, forthright and complete with FDA in all information regarding NDA 5-319 (*Pantopaque I) and that it was a crime for any sponsor to make fraudulent and/or misleading statements to FDA about a product marketed in the US.

FDA's Drug Efficacy Study Implementation (DESI) and Pantopaque

Uncertain about the safety of America's drug supply continued even after the passage of the Kefauver-Harris Amendments. As a result, Congress opened hearings in March 1964, chaired by Representative L.H. Fountain, to investigate FDA's efforts to promote drug safety. But Fountain's hearings took a comprehensive look at the agency's regulation of drugs, especially those that were removed from the market.

To further comply with the requirements of the drug amendments of 1962, FDA contracted in 1966 with the National Academy of Sciences/National Research Council (NAS-NRC) to study all drugs approved from 1938-1962 from the standpoint of efficacy. All drugs on the U.S. market would have been reviewed for both "safety"and "efficacy". Following the passage of the amendment, there was a legal time delay in enforcement by the Agency while the courts determined whether demonstration of "marketing success" met the requirements of valid proof of product "efficacy" according to the FDCA. The courts in 1970s ruled that marketing success alone did not constitute valid documentation of efficacy.

The review process begun by the FDA was called the Drug Efficacy Study Implementation(DESI). The Drug Amendments had required that the DESI be completed within two years and that all labeling recommendations be fully implemented by 1972. However, elements of the DESI process still continues in 2002.

DESI evaluated over 3000 separate products and over 16,000 therapeutic claims. The last NAS/NRC report was submitted in 1969, but the contract extended through 1973 to cover ongoing issues. The initial agency review of the NAS/NRC reports by the task force was completed in November 1970.

One of the early effects of the DESI study was the development of the Abbreviated New Drug Application (ANDA). ANDAs were accepted for reviewed products that required changes in existing labeling to be in compliance. In September 1981 final regulatory action had been taken for 90% of all DESI products. By 1984, final action had been completed on 3,443 products; of these, 2,225 were found to be effective, 1051 were found not to be effective, and 167 are still

pending. In May 1972, the DESI process was extended to cover over-the-counter (OTC) products.

Lafayette Pharmacal's NDA 5-319 was a drug products to come under review of the NAS-NRC DESI program as documented by Lafayette Pharmacal, Inc.s' receipt of the May 23, 1971 letter from FDA's Director of DESI Project Office, P. Bryan, M.D.. The DESI letter echoes the earlier 1969 labeling requests from FDA.

During the 1970s, the FDA started two new forums to help increase drug communication to the public. The Bureau of Drugs launched the FDA Drug Bulletin in 1971. The National Drug Experience Reporting System also was begun in 1971. The NAS had been studying the problem of not only how to catalogue and store information about adverse drug reactions, drug abuse, and drug interactions, but also how that information could best made available to health professionals. The study concluded that since the FDA had already begun to collect the drug data, that they should take the lead on creating and maintaining the adverse event reporting system.

In July 1979, FDA also proposed a program to provide patients with additional information about prescription drugs, including a description of the drug's uses, risks, and side effects. Under the Agency's proposal, all drug manufacturers would print the information and the health provider would give the insert to the patient. But, by September 1980, under the weight of well-organized opposition to the program, the FDA was forced to drop the requirement for a patient insert.

Pantopaque clinical literature had been reviewed by the **NAS-NRC Panel on Diagnostic Agents**. The indication for the drug was for myelography, and DESI advisory panel concluded that it was "effective" for that labeled indication. The comments of the DESI review summarized the information found in the published literature:

> Pantopaque (ethyliodophenylundecylate with 30.5% iodine in oil) has been widely used and is accepted as the current agent of choice in myelography. Comparative studies are few, but one in cats showed Pantopaque to be superior. Several groups have increased the dose without untoward effects. Small volumes (2-3 cc) of Pantopaque have been used also for positive-contrast ventriculography.

In terms of the labeling review, the advisor panel reviewed Pantopaque labeling that had been submitted and "cleared" by FDA in the NDA for marketing of Pantopaque in the U.S., the general comments by the members of the advisory panel for labeling of Pantopaque were as follows:

> **Additional side effects should be mentioned**:
>
> Infrequently, severe arachnoiditis has followed the intrathecal injection of Pantopaque, producing headache, fever, meningimus, severe back pains, pain in the lower extremities, and elevation of the white cell count and protein content of the cerebrospinal fluid. The incidence and severity of this arachnoiditis are greatly increased when active subarachnoid bleeding has been induced by the lumbar puncture.

Rare instances of lipoid granuloma, obstruction of the ventricular system, and venous intravasation producing pulmonary embolization have followed the intraspinal injection of Pantopaque.

Diagnostic tests of thyroid function involving the administration of radioactive iodine may be invalidated for many years, following the intrathecal injection of Pantopaque.

Additional contraindications should be mentioned:

The intrathecal administration of Pantopaque should be deferred if active subarachnoid bleeding is encountered in the performance of the lumbar puncture.

The administration of Pantopaque is contraindicated in patients with known hypersensitivity to iodine or its compounds.

The following phrase in the package insert is **incorrect**:
"The small amount of material that is left is usually absorbed within two months." In fact, the residual contrast medium in the subarachnoid space **usually remains for many years. This incorrect statement should be deleted.**

It should be specifically recommended that as much of the Pantopaque be removed from the subarachnoid space as possible, after the examination is completed.

The amount of Pantopaque commonly used is 3-12 cc rather than that quoted in the brochure (3-5 cc).

The recommendation in the package insert for the examiner to become "dark-adapted" before fluoroscopy is no longer applicable for many institutions where image intensification is used.

Pantopaque may be used in small volume (2-3 cc) for positive-contrast ventriculography when conventional air ventriculography is unsuccessful.

V. Marketing of Pantopaque (30%) following withdrawal of Pantopaque II's NDA

April 18, 1969 letter from Frank Gollon, Eastman Kodak Legal Dept, Trademark Section, to Mr. W.T. French, Patent Dept, Kodak Office:

> You have requested information concerning our marketing of ethyl iodophenylundecylate which is distributed by others as a contrast medium for radiography under the trademark PANTOPAQUE. I am advised that this information is required in connection with an inquiry received by Eastman Kodak Company from the United States Department of Justice which has challenged certain restrictive provisions in a patent license agreement relating to radiopaque (United States v

Sterling Drug, Inc. and E.R. Squibb & Sons, Inc.)

I understand that ethyl iodophenylundecylate is purchased from us by Lafayette Pharmacal Inc. who packages it in dosage form or vials for use as a contrast medium for radiography. Lafayette in turn sells the repackaged product to a number of distributors including General Electric Company, Picker X-Ray Corporation, Standard X-Ray Company, E.M. Parker Company, Kelley-Koett Manufacturing Company. In order that Lafayette may identify its product under our trademark PANTOPAQUE, we licensed that company in 1943 to use our mark upon the product sold by us to it under such trademark PANTOPAQUE. It is my understanding, however, that our sales of the chemical to Lafayette have been under the generic chemical name for many years now, probably dating from before 1957. Since PANTOPAQUE would be distributed by such other companies as General Electric, Picker, Standard, etc. in packages carrying neither the Lafayette not the Eastman Kodak name, it was deemed advisable to protect our proprietary interest in the mark, to also license these other companies to use the mark.

Your copy of the Department of Justice letter of inquiry addressed to this company is returned herewith.

February 11, 1970, Eastman Kodak Company, finalized the development of a process for manufacturing Ethyl Iodophenylundecylate (Pantopaque) that found a substitute for benzene in the esterification process to eliminate the health hazard associated with use of **benzene**. The process was titled Manufacturing Controls for the Preparation of Pantopaque and began:

There are no changes in the information previously submitted to the Food and Drug Administration, except that iodic acid was indicated as the iodinating agent. Actually, iodine is the iodinating agent and iodic acid is an oxidizing agent for regenerating iodine from the hydrogen iodide that is liberated, thus permitting complete use of the iodine.

It is noted that the instructions for items 6,7 and 8 of the current New Drug Application Form (F.D. 356 H) apparently contemplate considerably more detailed information than that which was originally required. .....

The manufacture and chemical purification of ethyl iodophenylundecylate is carried out in the Synthetic Chemicals Division located in the Kodak Park Division of Eastman Kodak Company in Rochester, NY. The manufacturing operations are carried out by trained, experienced chemical operators , chemical technicians and professional chemists employed by the Synthetic Chemicals Division. Quality Control operations are carried out by analytical technicians and professional chemists assigned to three Kodak Park areas- Synthetic Chemicals Division, Industrial Laboratory and Kodak research Laboratories.

W.S. Bucke , Lafayette Pharmacal, Inc. wrote Mr. J. Robinson, Legal Department, Eastman

Kodak Company on February 18, 1971 the following:

> Pursuant to our conversation, I wish to advise that your company **Kodak, Distillation Products Industries division**,(* bold and underlining added for emphasis) is responsible for meeting the U.S.P. requirements for Iophendylate Injection.

A proof of an advertisement for George Banta Company, Inc. intended for the Journal of Neurosurgery, August 1969 for marketing of Pantopaque. The advertisement discussed the use of Pantopaque contrast medium for the visualization of a large neurofibroma (*tumor) at the level of the third cervical vertebra.

> **Side Effects**: Clinical reports indicate that the incidence and the severity of the side effects following Pantopaque myelography with aspiration of the medium is but slightly greater than with ordinary lumbar punctures. (*Underlining added for emphasis). In 10-30 percent of such cases there may be transient symptomatic (*Underlining added for emphasis). reactions consisting of slight temporary elevation and increase of symptoms referrable to a back condition. When the medium is not removed, similar transient side effects (*Underlining added for emphasis). occur with a slight elevation of temperature in a greater percent of patients. To reduce the reactions to minimum and to facilitate the absorption of the medium, the bulk of the Pantopaque should be removed by aspiration after myelography.

The implication from the advertisement is that for a physician to reduce the risk of **transient** fever following myelography, they should attempt to remove the bulk of Pantopaque, but that if the agent is left in the spinal cord similar transient side effect may occur in a greater percentage of patients. This labeling does not reflect the results of long-term animal testing for Pantopaque when the contrast medium is left in the spinal column, nor the occurrence of permanent long term complications such as "obliterative arachnoiditis" in patients that has been reported within the medical literature, nor does it reflect the concerns that had been expressed by the FDA. This labeling also implies the Pantopaque has been cleared by FDA for visualization of a tumor in the cervical spine.

The letter from October 3, 1972 John Potts, of Eastman Kodak to Mr. Strawbridge, Picker Corporation, demonstrated just how closely Eastman Kodak monitored the Pantopaque trademark. It is unforunate that Kodak did not monitor the "accuracy and truthfulness" of the contents of the labeling in terms of patient safety. Regarding the license to use the trademark Pantopaque, Mr. Potts wrote:

> Our attention has recently been directed to the sales carton you are currently using to merchandize the Picker Myelogram Tray. Although this is a most attractive carton, we are somewhat concerned that the treatment afforded our PANTOPAQUE mark is not in compliance with the terms of our license agreement dated August 24, 1943....
>
> In the first instance, the legend "Trademark PANTOPAQUE Licensed by Proprietor", does not appear thereon. We believe such a legend is imperative to avoid any

misunderstanding as to the ownership of the PANTOPAQUE mark, and request that it be added as soon as possible to the main face panel of the carton–preferably, immediately beneath the most prominent impression of the mark.

Secondly, although the mark PANTOPAQUE appears some eight times on the carton, the proper generic terminology appears only once.....

Finally, it is noted that the carton in question does not contain one of the accepted legal notices of trademark registration as required by the license.....

We realize, of course, that your company would not intentionally do anything to jeopardize our rights in the PANTOPAQUE mark and know that you will take prompt action to correct the packaging in question.

In terms of demonstrating the working role and oversight of Eastman Kodak over Lafayette Pharmacal's product and product labeling, there was a January 31, 1973 letter from Eastman Kodak Company's Executive Vice President, International Photographic Division, written for the approval of Mr. Bucke of Lafayette Pharmacal:

It is our understanding that your firm wishes to distribute and sell in Mexico, packages and vials of contrast medium for radiography under our registered trademark PANTOPAQUE (Mexican Reg. No. 163,727). Accordingly, by this letter, we hereby grant to you a nonexclusive, nonassignable license to use said trademark in Mexico subject to the following terms and conditions which are necessary to protect our rights in and to said trademark PANTOPAQUE and the good will assocaited therewith:

1. Said trademark PANTOPAQUE will be used by you only on radiographic contrast media manufactured and sold by us to you; all such product to conform to standards of quality and sterility prescribed and approved by us.

3. We shall have the right of approval of all such product, packages and labels and you agree to furnish to us upon request, production samples of same for our inspection.

4. You, at all times, will acknowledge our ownership of an rights in and to the trademark PANTOPAQUE as applied to radiographic contrast media and similar goods.

.

Purchase of Lafayette Pharmacal By Alcon Laboratories

A Marketing Assessment report of Pantopaque sales 1976-1977 conducted by Alcon Laboratories had sales of Pantopaque accounting for 82% of Lafayette product sales. Phone interviews conducted with radiologists confirmed that Pantopaque was the only contrast medium currently

being used for myelography. Two radiologist interviewees mentioned a new aqueous preparation on the horizon that was under investigation but that had yet to be released by the FDA. In terms of amount of Pantopaque used for myelography, the 3 cc ampules had been losing sales ground to the more recently introduced 6 cc and 12 cc ampules.

Sales by Lafayette Pharmacal were to the major distributors such as Picker, G.E., Litton and are 50% of the list price. According to Mr. Griggs of Lafayette, Picker sales accounted for 50% of the product sales. Using extrapolation, Picker had purchased $1,750,000 of Pantopaque which it would have sold for $3,500,000. Since Lafayette personnel did not actively sell Pantopaque to radiologists, a gradual approach to phasing out Pantopaque distributors could potentially permit Alcon to convert most of the business to direct sales through LPI within 2 years.

There was also a statement that there appears to be a certain amount of receptivity medically to an aqueous product which is still under investigation. Regarding the assessment of the potential impact of the availability of water soluble contrast medium:

> It may never be approved by FDA but if it is, it could nibble into our 100% marketplace position.

The assessment concluded:

> On balance....no marketing considerations have presented themselves to preclude our moving forward on the acquisition. We will not double sales in one year by cutting out distributors quickly, but we do have much room to maneuver company sales to a substantially higher level within 2-3 years.

November 7, 1977 Alcon Laboratories, Inc. made a Proposal for Acquisition of Lafayette Pharmacal, Inc. for a purchase price of $8-10 million partially offset by excess cash and marketable securities of approximately $1.0 million held by Lafayette. Lafayette was a small company that specialized in x-ray contrast media, employed 30 people, and was located in Lafayette, Indiana. Stock purchase and sale was finalized January 1, 1978.

In terms of Alcon's assessment, the striking feature of Lafayette Pharmacal was the simplicity of the business. The company bought barium sulfate from a supplier in Germany and compounded it into various powder and liquid forms for distribution. Pantopaque had a single ingredient that was purchased from Eastman Kodak Company. Lafayette conducted manufacturing operations that consisted of sterilization, filtration, filling and packaging. Lafayette maintained no sales force and there was no competition at the time for purchase of Pantopaque.

> Lafayette has been a stable, highly profitable company for many years. The opportunity for purchase at the present time is related to Lafayette's principal owner, William Bucke, who is elderly and in failing health. He and the two other major stockholders Wm. Griggs and A. Kunz are at a point where they must continue the business as a small operation; go public to acquire funds, establish a sales force and expand the business; or sell the business to a company who already has a sales force,

effective R&D, and capable management and can capitalize on Lafayette operations.

(*Note: Water soluble contrast medium: Metrizamide was first cleared by FDA for marketing in mid-1978 sponsored by Winthrop Laboratories. Amipaque was a noninoic water soluble agent intended for regional and full column myelography. It was marketed as a lyophilized powder with diluent for reconstitution prior to injection. Because of its non-ionic structure and water solubility, it was absorbed from the CSF into the blood stream better than Pantopaque with approximately 60% of the administered dose excreted unchanged in the urine within 48 hours. Thus removal after myelography of Amipaque was not necessary. This "important difference" became an important selling point for the agent when it was compared to Pantopaque. Since Amipaque was also a low viscosity agent, it demonstrated better filling and x-ray delineation of nerve roots than Pantopaque.)

On September 8, 1978, Gerald Hect, Ph.D., Corporate Director of the Pharmaceutical Sciences, Alcon wrote to A Kunz, Ph.D., Technical Director of Lafayette Pharmacal regarding the changes that were to occur at Lafayette Pharmacal. Alcon requested an introductory statement to clarify the full strategy of Lafayette's R&D program in the areas of myelography and lymphography. Alcon also wanted Dr. Kunz to summarize Lafayette's plans for conducting safety testing. It was Alcon's policy that all safety testing must be coordinated through Corporate Toxicology, Dr. C A Robb, for approval prior to commencement.

Alcon requested that Dr. Kunz highlight Lafayette plans for future government submissions and the time that would be required. Lafayette must now deal with the Alcon Regulatory Affairs Division for all FDA submissions. In terms of Lafayette's R&D plans:

> Art, I feel your Research and Development plans ought to reflect, beyond a shadow of a doubt, Lafayette's major commitment to support and defense of your breadwinner, Pantopaque. Your communication of August 18 lists two projects in this regard. The first, Pilot Plant Synthesis of Iophendylate, is primarily a product support measure which has profitability implications. Pantopaque should be strongly considered as a prime candidate for synthesis and final dosage form manufacture in Puerto Rico where our tax advantage will return significantly more revenues to us than this activity conducted stateside would.
>
> The only other activity which I can identify as being truly in support or defense of Pantopaque is the activity which has an objective the Development of a Myelographic Technique Booklet for Radiologists. We view this specifically as "Marketing Services". The other two projects outlined in your communication of August 18 we do not consider as truly supportive or defensive of Pantopaque, but more appropriately as new programs for second generation myelographic agents. This would be your oily contrast agent and your non-ionic water soluble contrast agent.
>
> To further concentrate on this support and defense of Pantopaque, I would suggest that you consider the advantage of conducting well-controlled clinical studies (admittedly in addition to those already in the literature) which would allow you to

> accumulate first-hand information on the comparative safety, efficacy and side effects of Pantopaque versus Metrizamide. Perhaps additional studies can be conducted comparing Pantopaque with perfluoroctyl bromide if the state of development of the agent should warrant such a study.
>
> Basically, what I am proposing here is collecting additional well-controlled safety and efficacy data on Pantopaque versus what I understand to be the next closest horse in the race, Amipaque.
>
> Art, beyond Pantopaque support and defense, it would be my recommendation to pursue at the program and project stage the first generation improvement of Pantopaque outlined in your August 18 plans, an oily contrast agent, followed closely by the non-ionic water soluble contrast agent, both for myelography.....
>
> I trust the foregoing will be of some help to you in understanding how we view approaching R&D for a subsidiary which has as a significant share of its income a single product or group of products. Needless to say, Pantopaque is the plum in this regard.

In 1978, the Lafayette Director of Organic Research and Development , as well as the Product Complain Coordinator was Barry Newton, Ph.D. Dr. Newton appears to have been assigned the official task of responding to inquiries and issues involving the clinical use of Pantopaque. Mr. Robert Sharp was Lafayette's Quality Assurance Director.

Alcon's Annual Research and Development Report of 1979 discussed the impact that the availability of Amipaque, a non-ionic water soluble contrast agent for myelography was having on the sales of Pantopaque. During 1979, Amipaque, which cost 5 times as much as Pantopaque, had produced a purported $20,000,000 in revenues for Winthrop and had redefined the myelography market. Price increases on the part of Lafayette Pharmacal had kept the dollar volume of Pantopaque stable despite the reduced number of units sold.

Dr.s Kunz, Newton and Hecht learned that Wintrop was working with Nyegard to develop the second generation of Amipaque that could be marketed as an aqueous solution. (Note:* NDA cleared 1/1/1982 as NDA 17-982 for Nycomed for Amipaque.)

Alcon's proposed R&D strategy for maximum impact, projecting that Lafayette R& D was at least 5 years away from NDA approval on an in-house developed non-ionic water soluble contrast medium:

> In order to defend our position with Pantopaque, an alternate source of supply is required. Our 1979 plans called for completing laboratory synthesis and scale-up with yield optimizations and acquisitions of equipment, facilities, and production costs. This activity was required due to our dependence on Eastman Chemicals as the sole supplier of this drug. All scale-up objectives and estimates were satisfactorily achieved and this project is nearing completion, at which time we will be in a position

to recommend a course of action to top management in this regard. Additional accomplishments included the definition of a final filter for Pantopaque (based on an FDA/Lafayette agreement in October) and the preparation of a revised labeling instructing its use for submission early in the 1st Quad 1980.

Overall, 1979 was a year for bringing Lafayette Pharmacal R&D firmly into the Corporate R&D organization, both philosophically and managerially. Such concepts as Unit Plans, Standards of Performance, Good Laboratory Practices and astute, tough-minded decision making regarding the expenditure of Research and Development resources have been implemented and enthusiastically embraced by Radiology R&D management and personnel.

June 28, 1979 letter from G. Hecht, Ph.D to Dr. B. Newton, Lafayette Pharmacal:

I am writing to reaffirm Corporate R&D position in your practices for the handling of medical complaints. It is our position that the R&D Director handle all complaints of a medical nature. We are therefore expecting you, as Associate Director of Lafayette Pharmacal R&D, to continue in this regard.

It would, however, be wise to document a formal understanding with a reputable radiologist and/or neurologist to obtain qualified medical opinion for complaint handling. In order to do so, I feel we should formalize an agreement with such consultants, place them on a retainer if necessary, obtain their curriculum vitae, etc., for our files to lend credence to their use as medical consultants.

June 29, 1982, Dr. Newton called Dr. Hecht as recorded on a Recent Information Form filed by Dr. Hecht. The point of issue was a paper appearing in the June issue of Radiology, p. 699 regarding the use of Pantopaque and Amipaque in monkeys.

Dr. Newton called to report the appearance of the subject article in Radiology, p. 699, June 1982. Upon reviewing this article, Dr. Newton felt that it was a very strong indictment of Pantopaque as a causative factor in arachnoiditis following Pantopaque myelography. Apparently the article was able to demonstrate striking differences between Pantopaque and Amipaque in primates (monkeys). This demonstration of arachnoiditis was made on gross observation followed by graded histology.

Upon discussion, Dr. Newton and I agreed that he would send the article to Dr. Sol Betnitzky, Neuroradiologist, Kansas City; Dr. Richard Gilmor, Neuroradiologist and Neurosurgeon, University of Indiana; Dr. Larry Gold, Neuroradiologist, University of Minnesota; Dr. Ling Lee, Neuroradiologist and Neurosurgeon, Veterans Administration Hospital, Nashville, TN; Dr. Jans Muller, a Pathologist at IUPUI in Indianapolis. These practitioners have had considerable experience in the use of Pantopaque and Amipaque and will be requested to provide us with their review of the findings as published by Dr. Haughton.

July 1, 1982 Dr. Barry Newton sent A. Kunz an inter-office memo regarding a Pantopaque article that had been issued by Johnston and Matheny regarding their study of 28 patients with **arachnoiditis**. The authors made the point that 4 of the 28 patients (14%) had myelography more than one year after spinal surgery and all 4 had "**severe arachnoiditis**". Microscopic studies of cyst walls containing Pantoaque (removed at surgery) did not show inflammatory changes any greater than other areas of the scar tissue. The authors had concluded that in most cases, arachnoiditis developed as a result of some traumatic event to the spine. These events included herniated disc, "myelography", surgery, or other injuries. The arachnoid then developed an aberrant healing process that was known as arachnoiditis.

July 14, 1982 Dr. Newton phoned Dr. Hecht regarding the initial results of the reviews of the Dr. Haughton's article. Two of the five physicians, Dr. Batnitsky and Dr. Gilmor had been impressed by Dr. Haughton's work and found the article "disturbing"; Dr. Muller had not reviewed the article; Dr.s Gold and Lee indicated that the article contained "nothing new", with Dr. Lee the most critical of Dr. Haughton's work.

(* Note: **Dr. B. Newton had supplied Dr. Haughton with 12 - 3cc vials of Pantopaque for use in his primate studies.** In a June 25, 1982 letter from Dr. Newton to Dr. Hecht, he indicated that Dr. Haughton's primate dose of Pantopaque was equivalent to a **3-12cc** intrathecal dose of Pantopaque in a human.)

July 16, 1982 Dr. Newton once again phoned Dr. Hect. Dr. Gilmor had felt the article was **quite damaging to Pantopaque**, however, he assured Dr. Newton he wouldn't be influenced by it and would continue to use Pantopaque. Both Dr.s Gilmor and Betnitsky indicated that Haughton's article did not address the clinical symptomatology associated with x-ray detected arachnoiditis. Based on the estimated millions of procedures done since the early 40's, it may be that the arachnoiditis remains subclinical in severity. Dr. Gilmor and Dr. Ling Lee had seen few severe reactions. Dr. Muller expressed no opinion. Dr. Gold continued to be supportive of Pantopaque and that the incidence of arachnoiditis was almost negligible. Dr. Gold had phoned Dr. Haughton and spoke to him personally about the content of the article. Dr Haughton had stated to Dr. Gold that he only said in the article what was already generally known and accepted, namely that if pantopaque is not removed completely it may produce arachnoiditis, and sometimes that arachnoiditis may be severe. However, Dr. Hect also indicated in his memo that Dr. Barry Newton was genuinely concerned about the contents of the article and was most anxious to sit down and discuss the article with Alcon's legal consul.

April 25, 1983 internal memo from Hugh Hunter, Laboratory & Specialty Chemicals Markets, HSMD, Eastman Kodak to W.J Prezzano with Dr. Barry Newton's name written in the margin. The memo demonstrates that Pantopaque's primary supplier, Eastman Kodak, was aware of legal activity involving the use of Pantopaque and also was aware of the agent's falling popularity with the medical imaging community. The Kodak memo stated:

> Relative to J.P.Samper's April 13 letter, we would like you to consider our proposal based on the following additional information.
> PANTOPAQUE is a mature product and losing market share to a competitive

radiopaque dye called Amipaque (metrizamide)-------1982 sales to end users showed a 40% increase for * Amipaque compared to a 16% sales decrease for PANTOPAQUE. Cost per examination for the two products is about the same $12.90 for PANTOPAQUE versus $13.00 for Amipaque. Amipaque has become the preferred radiopaque dye for non-traumatized spine. Recently Amipaque is being touted for use in cases with spine trauma. (See enclosed article)

Based on the above information we would propose the following:
1. Raise the price of PANTOPAQUE to our customers in a two stage format. Since we are on a quarterly system of changing prices to our bulk chemical customers, we would like to announce a first increase of 8.7% on * June 1 with an effective date of July 1, 1983, and a second increase of 6.3% December 1, 1983, with an effective date of January 1, 1984.

Monitor the legal activity and submit a biannual report January 1 and July 1 enumerating the **outstanding legal cases**,(*Bold added for emphasis). the costs associated with each of them, and indications as to the urgency of each case.

April 27, 1983, Dr. Barry Newton, now identified as Director of Sales & Marketing for Lafayette wrote to R.A. Sharp regarding his "recommendations" for revisions to the Physician Package Insert for Pantopaque. The revisions appear to be very much in keeping with Dr. Newton's proposed new marketing strategies for expansion of the use market:

On the next revision of Pantopaque I would recommend that the following two changes be made. In the section under "Use of Pantopaque" we use the phrase "particularly suitable for lumbar myelography." This phrase should be withdrawn from the package insert. Under the Reactions section, we should use the phrase "**occasionally severe arachnoiditis may occur**." (*Bold added for emphasis). This should be changed to read simply "**arachnoiditis may occur**."(*Bold added for emphasis). We should also add the phrase "**arachnoiditis may be more frequent if Pantopaque is used after surgical intervention**".(*Bold added for emphasis). A reference citing this should be included.

On the same day, April 27, 1983, Dr. Newton sent a memo to Manufacturer' Sales Representatives providing a Pantopaque reference that discussed some of the medical indications, i.e. cervical spine, that may be suitable for the use of Pantopaque. The point being made by Dr. Newton was that the representatives should make the doctors in the neuroradiology department aware that Pantopaque was not associated with seizures and that is why it was recommended in an article on cervical myelograms done in patients with cervical trauma.

With Amipaque, because of their fear of seizures or convulsions, doctors should have a concern about using Amipaque in cases where the patient's spine is injured. The article by Dr. York Chynn talks about the technique for the introduction and removal of Pantopaque. Dr. Chynn has done at least 5000 Pantopque myelograms without any serious side effects. He is a firm believer that the problems that are reported on

> Pantopaque are due to **technical procedure problems**. (*Bold added for emphasis). Whenever you are in a radiology department and have an opportunity, I would like for you to check to see if the pharmacy has Pantopaque in stock. If possible, also provide the neuroradiologist with copies of the enclosed articles.
>
> Because of the commission payments that have been established with Lafayette and your company, Pantopaque does represent a major portion of the commission, and **it would be to your benefit to support this product as much as possible.**(*Bold added for emphasis).

May 24, 1983 Lafayette Pharmacal's Dr. Barry Newton, General Manager of Lafayette Pharmacal, finalized a consulting agreement between **Dr. York Chynn** and Lafayette Pharmacal regarding his providing professional support for promotion of Pantopaque. Lafayette Pharmacal agreed to pay Dr. Chynn for pictures, drawing and a written procedure for performing Pantoaque myelography that was to be completed by October 1, 1983. Lafayette also agreed to pay for time and expenses of Dr. Chynn for writing an article regarding a safe procedure for Pantopaque myelography that was to have been accepted prior to December 1, 1983 for publication in any one of the following journals: Neuroradiology, American Journal of Roentgenology or Spine.

May 27, 1983, Dr. Newton issued an inter-office correspondence to Frank Buhler regarding his recent trip to Indianapolis for discussions with Dr.s R. Miller and D. Maglinte regarding barium enema technology, including E-Z-Em devices, and **Dr. R. Gilmor** regarding his potential writing of an article for Lafayette about Pantopaque myelography. Concerning Dr. Gilmor, Dr. Newton wrote:

> Dr. Gilmor and I discussed the possibility of a paper on Pantopaque myelography. I pointed out to Dr. Gilmor that an article dealing with the avoidance of intravenous injections of Pantopaque, as well as overcoming some other objections to Pantopaque, might be appropriate. Dr. Gilmor agree to prepare an outline on a possible publication. The understanding was that I would review the article, and it must meet my approval before it would be submitted for publication. Dr. Gilmor noted that in light of the strong advocates for water soluble myelography on the review committees of the journals, it may be difficult to get a publication in favor of Pantopaque approved. This was very positive meeting, and I feel confident that Dr. Gilmor will prepare an article acceptable by us. **I indicated to Dr. Gilmor that we would pay expenses for him and his wife to attend a meeting dealing with neuroradiology (ca. $2500).**(*Bold added for emphasis).

During 1983, Dr. Newton began to increase the visibility of Pantopaque in terms of advertising to physicians. For example, Lafayette issued a June 30, 1983 mailing directly to physicians:

> Dear Doctor:
> ARE YOU DOING MEYLOGRAPHY?
>
> If so, please take a brief moment to review the enclosed product information sheet on Pantopaque. Pantopaque has been in use for myelography in the United States since

the 1940's. During that time, Pantopaque has been used for several million myelograms and the incidence of side effects has been **extremely low**.(*Bold added for emphasis). If you are not currently using Pantopaque, this may be a good time to reevaluate it as a myelographic agent for your department.

May 4, 1984, Dr. Newton issued a confidential sales program packet for Pantopaque to "All Sales Representatives" that included Dr. Chynn's article, and anatomical drawings of the spinal cord, Amipaque and PantoPaque inserts.

PANTOPAQUE MYELOGRAPHY PROVEN OVER AND OVER IN MORE THAN FIFTEEN MILLION EXAMS
EFFECTIVE
FLEXIBLE
FAST
VERSATILE
ECONOMICAL
PREDICTABLE

Major Themes:
1. PantoPaque has been in continuous use since 1944. More than 15,000,000 myelograms have been performed.
2. PantoPaque is a very safe and effective myelographic agent when used properly. It can be safely used for whole column myelography.
3. With DRG's , perhaps this would be a good time for the hospital to reevaluate their use of PantoPaque. **The PantoPaque for a myelogram consts about 50% of Amipaque ($45.00 vs. $100.00).**(*Bold added for emphasis).
4. Before Amipaque was introduced, there was **no listing in Index Medicus for "Myelography- Side Effects"**,(*Bold added for emphasis). now there is a special heading for side effects and these are nearly all Amipaque.
See attached.

PantoPaque Usage:
PantoPaque is packaged in single dose glass ampuls because PantoPaque is deleterious to rubber seals.

After opening the ampuls, Lafayette recommends that PantoPaque be filtered through a **Gelman 5 Micron Acrodisc filter.**

Ordering Information:

For 1984, Lafayette is paying a 3% commission on all direct orders that are written by MSR's or that specify....as per "Your Name"...on the order. You can give a 5% discount on individual direct orders of $500 net. We do not want to make your key distributors angry by taking business away from them. But, if you find that a hospital buying Pantopaque from a distributor, that is not helping you, then you should try to take that order direct.....

May 24, 1984, Walter Hauck, DVM, **Hazleton Laboratories** wrote to Ms. Aracelis Ramirez, Alcon Laboratories PR, Inc. to inquire whether they could have Alcon's permission to publish an article in a laboratory animal science journal regarding their **observations of clinical disease and deaths in their pyrogen rabbit studies done with intravenous injection of Pantopaque**. Hazelton Laboratories wanted to know how the material should be identified in the article. June 12, 1984 O.J. Lorenzetti, Ph.D. of Alcon Ophthalmology-Surgical responded to Lee Hansen, President/ General Manager of Alcon regarding the request from Hazleton Laboratories:

> Research and Development does not support publication by Hazleton of data acquired through our contracts on pyrogen testing of Alcon's radiopaque product.
>
> We must refuse this request since it cannot benefit Alcon in any way and may prove to be damaging to our product.
>
> In your reply I recommend a simple decline of request, as being inconsistent with company policy as well as a violation of client relationship. In the future you may wish to supply test samples, for analysis by contract laboratories in a masked fashion providing only the guidelines of amount to be injected/tested.

July 18, 1984 Mr. Hansen received a memo from Mrs. Maria Santiago detailing a July 18, 1984 FDA visit from FDA investigator, Mr. Andres Toro, **San Juan District Office**, of Alcon's Humacao, Puerto Rico Alcon facility. **Alcon** was presented with a FD Form 482 for collection of data regarding parenteral products in a nationwide survey. FDA's inspector indicated that the purpose of the FDA's survey was to determine whether significant changes had been made in parenteral product formulations and the types of complaints that had been received over the last two years. Apparently the Puerto Rico site was now manufacturing **Pantopaque**, with Alcon responsible for filter sterilization and filling the ampules. The raw material supplier was still Eastman Kodak, Kodak Park Works, Rochester, NY. **FDA inquired whether there had been NDA changes involved.** Alcon's personnel responded yes, namely the following two changes:
1. Change in sterility testing Standard Operating Procedure to membrane filtration.
2. Labeling change to provide for change in Corporate signature.

Other changes recorded in the memo included the placement of a caution statement in the product insert for use of plastic syringes. The dates of manufacturing of last lot released, lot code and expiration data was Lot Code= 2-HCBM, Expiration Date 3/89, Manufactured March-1984. FDA collected specimens of labeling used during the previous year as well as current labeling. Product complaint files of 1982, 1983, and 1984 were reviewed. FDA specifically requested a copy of the **complaint summary page for three complaints.**

> Noted that two of the 1983 complaints referenced patient reaction. Asked if these complaints were reported to FDA. It was explained to him that these complaints were not included in the product annual report, since the reactions are already included in the product labeling and the frequency is not considered abnormal.(*Underlining added for emphasis).

No further comments were made and the inspection was concluded.

No 483 was issued.

Meanwhile, September 10, 1984, Dr. Newton provided All Lafayette Sales Representatives with a copy of an June 1984 Neurology article by Dr. Meador, et al., that dealt with 2 cases of **irreversible spinal neurological deficits following myelography with metrizamide (Amipaque)**

> You should maintain a copy of this article in your presentation materials so that when you are discussing PantoPaque with a physician or technologist, reference can be made to this article pointing out the **safety of PantoPaque** (*Bold added for emphasis). versus Amipaque.

April 29, 1985, Mr. Poe of Alcon Laboratories received an irrate letter for Ms. Gaylene Tsipis, Coordinator, Technical Drug Information Services, **Drug and Poison Information Control**, Ohio who had also forwarded a copy of her letter to Kay Pearson, Chief, FDA, Division of Drug & Biological Experience, **Reports Evaluation Branch**. Ms Tsipis wrote:

> I recently had an occasion to contact Alcon Laboratories regarding information about a possible adverse drug reaction (paralysis of the lower extremities) to Pantopaque. I had already called Lafayette Pharmacal and was told that your company actually manufactured the drug. There seemed to be much confusion regarding who, if anyone, could give me information in the incidence and nature of this adverse reaction. Since the company should have both their own clinical trial data and current adverse reaction reports as information sources, I was disconcerted that this information did not seem to be readily available nor did there seem to be any interest in documenting this possible adverse reaction to one of your drugs. A representative of the company did finally call the hospital involved but the apparent "run around" was very frustrating and time consuming considering the potential seriousness of this patient's situation
>
> I am writing this letter out of concern over the apparent lack of organization and inability to obtain timely information of a product that has the potential for some severe side effects/adverse reactions.
>
> I hope future calls to your company regarding one of its products will be handled more expeditiously.

Ms. Tsipis also sent a letter to Ms. Ann Fox, Lafayette Pharmacal regarding the same issue:

> On April 1, 1985, I had an occasion to contact Lafayette Pharmacal regarding information about a possible adverse drug reaction (paralysis of the lower extremities) to Pantopaque involving a patient in a local hospital. While the 1985 American Drug Index lists Lafayette as the manufacturer of this drug, your company would not accept

> a collect call to report this potential problem and when I finally was able to talk to you I was told that, in fact, Alcon Laboratories Inc. made the drug and not Lafayette. You offered to either have someone from your Quality Assurance department or someone from Alcon call me regarding the situation. I was not contacted by anyone from either company and subsequently had to call Alcon myself.

October 2, 1985, Ms. Tsipis' letter was referred within FDA to B.R. Stonecipher, Director of the Division of Drug Quality Evaluation who sent copies to the Agency's Directors, Division of Onclolgy and Radiopharmaceutical Drug Products and Division of Drug and Biological Experience with the following question:

> Lafayette Pharmacal markets Pantopaque Injection which is manufactured by Alcon Laboratories.
>
> Attached are copies of letters from the Drug and Poison Information Center, Cincinnati, Ohio, containing remarks to a report of an adverse reaction.
>
> Do your Divisions have any reason to believe that either Alcon or Lafayette are not properly handling or reporting drug reactions or adverse experiences related to their Pantopaque product?

June 2, 1986, FDA memo by A.E. Jones, MD to the Agency's record regarding intrathecal Pantopaque:

> Dr. Nissel has spoken of his concern about the chronic effect of pantopaque (intrathecal). Dr. Palmer and I discussed whether some action concerning this chronic effect should be taken now that other agents are available for myeolography. He advised that we explore the annual usage of Pantopaque- from the annual reports. Marc Anderson reported the following yearly distribution:
>
1977-78	7200 l	1980-81	2570 l	1984-85	958 l
1978-79	6500 l	1981-82	2943 l		
1979-80	4600 l	1983-84	1617 l		
>
> Dr. Palmer was advised of this **declining usage**. (*Bold added for emphasis). He recommended that further action **would probably not be necessary** (*Bold added for emphasis). as Pantopaque was gradually being replaced as an intrathecal agent by the newer non-ionic agent.

The agency's memo is of interest in that in 1986 the FDA's reviewers appeared to have viewed the safety concern for "chronic effects" of intrathecal pantopaque as a **fading issue of concern**. Pantopaque as a product was seen by FDA as rapidly exiting the myelography market with the increased availability of other products. Therefore, the agency in 1986 determined not to view dealing with pantopaque's chronic issues as a **high priority issue** in terms of future assignment of FDA's manpower and resources. The declining U.S. market would take care of pantopaque.

June 18, 1987 a labeling review of Pantopaque was conducted by Alcon's staff and documents the

uncertainty with which they attempted to begin to create adequate and informative labeling for Pantopaque. The agenda for the Alcon meeting included a review of the drug experience complaint record. For the previous year there had been "13 patient complaints" recorded that included arachnoiditis, focal seizure, burning in the lower back, nausea, allergic phenomenon, suspected meningitis- but was not considered as product-related. There was no mention whether any of these reports were filed with FDA as adverse events as required by FDCA, or if the number 13 reflects only the number of complaints filed with FDA, and not the number of patient complaints actually received.

In terms of the 1986-1987 medical literature, Dr. Lorenzetti, after reviewing the literature indicated that there had been "nothing new". In terms of their legal review, there was one suit pending in appeal with another not yet filed in Dade County, Florida. The recommended action for the meeting was to send the labeling review comments to Dr. Corsica for further comments. The new labeling was to be available by November, 1987.

> Labeling changes:
> Adverse Reactions: (Add) Severe arachnoiditis has been reported.
> There are the following handwritten notes:
>
> ? statement that patient should be injected only by personnel trained in proper technique for injecting and removing pantopaque.
>
> * Should we say Pantopaque is a 2nd line medium? It does have increased % of arachnoiditis-so state? Use when conditions of a patient make administration of water solubles contraindicated or otherwise dangerous.
> ADRs
> -Table listing % of reactions
> [Put comment about increase % complications with patients with multiple sclerosis . Kaufman, Lancet 1976 in warnings, or precautions]
>
> Note especially the incidence of arachnoiditis (This is the primary side-effect used as an argument against Panto.) What to do to minimize its risk, I question need to list symptoms associated with arachnoiditis?
>
> No need to note arachnoiditis again under "rare instance"...
> Removal of Pantopaque
> ?Note that attempted complete removal is very improtant to decrease risk of arachnoiditis.
>
> I am not familiar with the mandatory inclusions for inserts. That would be helpful.
> Differences between warnings/precautions?

August 17, 1987, John Spurill, Vice President, Surgical/Specialty Alcon, seeing the declining Pantopaque market, sent a memo to Lee Hansen, General Manager and President of Alcon that stated:

> After careful analysis of the future business prospects for Pantopaque, the current

Pantopaque inventory levels and the offer for raw material from Kodak, we have come to the following conclusions.

-We should inform Kodak we are not interested in an additional raw material.

-We should maintain all existing finished goods and work in process in anticipation of future Pantopaque orders. Lafayette has indicated a need for 3 ml during 1987.

- We should explore alternatives for disposing and or other uses for the Pantopaque equipment, as no further production other than packaging of existing worked in process is planned.

Therefore, as of 1987 , Alcon management had determined that they would silently withdraw from active Pantopaque manufacturing and marketing. There would be no legal requirement for a manufacturer to notify FDA of a marketing decision to withdraw a product from the US market due to declining use. Pantopaque was NOT being "recalled" from the market to address issues of safety and effectiveness, and the firm did not consider the product to be in violation of the FDCA. Pantopaque product made in 1987 would have a product shelf life through 1992. Alcon's plan was to continue to sell Pantopaque to the medical community for imaging until the existing stock was depleted and/or expired. FDA would not have been informed that there were any "safety issues" with Pantopaque and if a new use were to resurface for the drug, the product could be legally reintroduced.

March 15, 1990, FDA's Division of Medical Imaging, Surgical and Dental Drug Products, Medical Imaging Group, headed by Robert West, with Dr. Dominick Conca as medical officer recorded a telephone conversation with Scott Kerbey , **Inside Edition**, an investigative reporter.

Mr. Kerbey originally had called FDA on March 14, 1990 to speak with Mr. West, but the phone call had been rescheduled for the 15th. Mr. Kerbey was calling FDA and Mr. West to inquire about a patient that had undergone at least three myelograms in the mid-1970s with introduction of the drug Pantopaque, who was now severely paralyzed with arachnoiditis. The patient had attempted to sue Alcon Laboratories, but had been unsuccessful since the statute of limitations had appeared to have elapsed.

Mr. Kerbey now contacted FDA and Mr. West because of a past communication between the patient regarding the possible occurrence of arachnoiditis and the occurrence of the risk in a 1970 package insert. Furthermore, Mr. West had indicated to the patient that in the early 1970s it would not be reasonably expected that the patient consumer would have been aware of the potential adverse reactions that may occur with a myelographic agent. Mr. West indicated to Mr. Kerbey that the occurrence of arachnoiditis had been present within the current package insert.

When Mr. Kerbey asked if there had been any other myelographic alternative at that time, Mr. West deferred his question to Dr. Conca, Medical Officer at FDA. Dr. Conca indicated that Pantopaque was the only "approved" myelographic contrast agent available in the U.S. in the

1970's for myelography. Mr. Kerbey asked whether there was a need for Pantopaque in today's clinical practice setting. Dr. Conca indicated that Pantopaque's use had declined significantly since the advent and wider use of newer water soluble myelographic agents. He stated that the drug may still have some limited clinical use, e.g., in those patients who require myeology and have had an adverse event secondary to the use of a water soluble myelographic agent, or in patients who have a spinal cord compression or spinal canal block. In the latter group of patients, it may be desirous to use a rather small amount of Pantopaque to help delineate the exact level of cord compression or spinal block, usually for an emergency or urgent therapy, and to determine relief of compression or block in follow-up to therapy. These patients represented a fairly ill population or a group with metastatic cancer to the spine and a reduced life expectancy. Therefore, to FDA there was still a clinical place for Pantopaque on the US market.

Dr. Conca indicated that Pantopaque was the only myelographic agent that required removal after diagnostic myelography. Some drug usually would remain within the spinal canal even after meticulous and appropriate myelographic technique.

In response to Mr. Kerbey's questions, Mr. West indicated that FDA's mechanism to inform the medical community about potential adverse reactions to drugs was through the package insert. FDA does not attempt to inform the general public directly about such potential adverse reactions, but would inform the public directly if adverse reactions occurred at such frequency or magnitude that public safety may be jeopardized. Mr. Kerbey was also informed that it was Mr. West's opinion that the **potential occurrence of arachnoiditis** was well documented in the myelography sections of radiological textbooks. Mr. West provided Mr. Kerbey with some literature citations found in the Pantopaque package insert.

Mr. Kerbey asked about the frequency of reporting adverse reactions for Pantopaque, especially arachnoiditis. Mr. West provided a list of reports that were present in the FDA's adverse event reports database through **March 1990.**

March 18, 1990, Mr. Kerbey called back to request a face-to-face interview with Dr. Conca and Mr. West at FDA. Mr. Kerbey was referred to direct his inquiries to FDA's Press Office.

Mr. West's search of adverse reaction reports filed with the FDA through March 15, 1990 from any source with the occurrence of "arachnoiditis" for "Pantoapque" produced 16 reports with the following breakdown: 9 females, 6 males, one sex unspecified;

1977-5; 1983-1; 1984-1; 1986- 2; 1987-4; 1988-3; and 1989- 4.

June 22, 1990, there was a FDA memo of a phone call made to FDA by Henry Sanchez, FDA District Office, New Orleans, LA regarding NDA 5-319:

> Mr Henry Sanchez of the FDA District Office called this division to get information on the contrast material Pantopaque (NDA 5-319). His concern was that the product had been mentioned on a television talk show hosted by Geraldo Rivera and he had received a request for further information from a consumer.

Dr. Eric Jones of this division explained the uses and side effects of the product and the current labeling was faxed to Mr. Sanchez.

September 26, 1990 Alcon Laboratories sent a 15 day report to FDA regarding NDA 5-319 regarding "**Increased Frequency Report**" (IFR):

Report Interval: March 1990- September 1990
Comparative Time Interval: February 1989- February 1990

Report of the adverse reaction of "**arachnoiditis**", during a comparative interval- 2 reports, the current report interval- **25 reports**.
Comments:
A class action suit naming **twenty-five plaintiffs** (*Bold added for emphasis). has been received with the allegation that the named plaintiffs "have suffered" and will suffer severe and permanent personal injuries, ranging from chronic pain to paraplegia, quadriplegia, and death from the severely painful, debilitating and incurable disease known as arachnoiditis.

*We are also aware of a report in the Wall Street Journal of August 30, 1990, page 84, which makes reference to a suit of **300 plaintiffs**.(*Bold added for emphasis).

FDA indicated on Alcon's information report for the IFR that the agency had no plans for further action in response to the IFR submission beyond continued monitoring of spontaneous reports.

In 1993, there were scattered articles in the U.S. medical literature that discussed the dilution of **anesthetic agents with Pantopaque for use in injected epidural anesthesia.** The pantopaque was added to help prolong the anesthetic effects of the drugs.

The Federal Register, August 5, 1996 **N61 FR 40649**, published **FDA's withdrawal of Approval of 87 New Drug Applications effective September 4, 1996.** One of the applications withdrawn by the agency was **NDA 5-319**, Pantopaque, manufactured by Alcon Laboratories, Fort Worth, Texas. FDA indicated that the holder of the withdrawn applications had notified the agency in writing that the drug products were no longer marketed by them and requested that the approval of the application be withdrawn.

In the U.S. medical literature, J. Vasc Interve Radiol, Nov-Dec; 11(10):1285-95, **Long-term outcome of embolotherapy and surgery for high-flow extremity arteriovenous malformation**, RI White, et al. from Yale University, there was a discussion of the use of a mixture of cyanoacrylate dilutes with either "iophendylate" or "ethiodized oil" (iodinized poppy seed oil) in 19 of 20 patients. No specific source for the materials was identified.

VI. Pantopaque's Labeling

Labeling: Selected Sections of FDA's 21 Code of Federal Regulations and Food, Drug and Cosmetic Act regarding Labeling and a Manufacturer's Responsibilities

21 CFR § 201.5 Drugs; adequate directions for use.

Adequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended. (Section 201.128 defines "intended use.") Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:

(a) Statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
(b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
(c) Frequency of administration or application.
(d) Duration of administration or application.
(e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).
(f) Route or method of administration or application.
(g) Preparation for use, i.e., shaking, dilution, adjustment of temperature, or, other manipulation or process.
[41 FR 6908, Feb. 13, 1976]

21 CFR § 201.6 Drugs; misleading statements.
(a) Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic.
[41 FR 6908, Feb. 13, 1976]

21 CFR § 201.56 General requirements on content and format of labeling for human prescription drugs.
Prescription drug labeling described in §201.100(d) shall contain the information in the format required by §201.57 and shall meet the following general requirements:

(a) The labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug.
(b) The labeling shall be informative and accurate and neither promotional in tone nor false or misleading in any particular.
(c) The labeling shall be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.

Conclusions based on animal data but necessary for safe and effective use of the drug in humans shall be identified as such and included with human data in the appropriate section of the labeling, headings for which are listed in paragraph (d) of this section.
(d)
(1) The labeling shall contain specific information required under §201.57 under the following section headings and in the following order:
Description.
Clinical Pharmacology.
Indications and Usage.
Contraindications.
Warnings.
Precautions.
Adverse Reactions.
Drug Abuse and Dependence.
Overdosage.
Dosage and Administration.
How Supplied.
(2) The labeling may contain the following additional section headings if appropriate and if in compliance with §201.57 (l) and (m):
Animal Pharmacology and/or Animal Toxicology.
Clinical Studies.
References.
(3) The labeling may omit any section or subsection of the labeling format if clearly inapplicable.
(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by §201.57(a)(1)(i), (ii), (iii), and (iv) and §201.100(e). The information required by §201.57(a)(1)(i), (ii), (iii), and (iv) shall appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(e) The labeling shall contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.
[44 FR 37462, June 26, 1979]

21 CFR § 201.100 Prescription drugs for human use.
A drug subject to the requirements of section 503(b)(1) of the act shall be exempt from section 502(f)(1) if all the following conditions are met:
(a) The drug is:
(1)
(i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription drugs; or
(ii) In the possession of a retail, hospital, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs; or
(iii) In the possession of a practitioner licensed by law to administer or prescribe such

drugs; and
(2) It is to be dispensed in accordance with section 503(b)

(b) The label of the drug bears:
(1) The statement "Caution: Federal law prohibits dispensing without prescription" and
(2) The recommended or usual dosage and
(3) The route of administration, if it is not for oral use; and
(4) The quantity or proportion of each active ingredient, as well as the information required by section 502 (d) and (e); and

(c)
(1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and...

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and §201.105(b)(2) contains:
(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 505 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted, under the provisions of section 505, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and
(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed.

[**40 FR 13998, Mar. 27, 1975**, as amended at 40 FR 58799, Dec. 18, 1975; 42 FR 15674, Mar. 22, 1977; 43 FR 37989, Aug. 25, 1978; 44 FR 20659, Apr. 6, 1979; 44 FR 37467, June 26, 1979; 45 FR 25777, Apr. 15, 1980; 63 FR 26698, May 13, 1998; **64 FR 400, Jan. 5, 1999**]

21 CFR § 201.128 Meaning of "intended uses".
The words *intended uses* or words of similar import in §§201.5, 201.115,201.117, 201.119,201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons'

expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.
[41 FR 6911, Feb. 13, 1976]

21 CFR § 314.81 Other postmarketing reports. [*Initial date for CFR citation- February 1985]

(a) *Applicability.* Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.
(b) *Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:
(1) *NDA-Field alert report.* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA-Field Alert Report."
(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.
(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application.

(2) *Annual report.* The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and **must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval** (* Bold added for emphasis) that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) ***Summary***. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.
(ii) ***Distribution data***. Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.
(iii) ***Labeling***. Currently used professional labeling, patient brochures or package inserts (if any), a representative sample of the package labels, and a summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.
(iv) ***Chemistry, manufacturing, and controls changes***.
(*a*) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.
(*b*)A full description of the manufacturing and controls changes not requiring a supplemental application under §314.70 (b) and (c), listed by date in the order in which they were implemented.
(v) ***Nonclinical laboratory studies***. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.
(vi) ***Clinical data.***(*a*) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.
(*b*) Summaries of completed unpublished clinical trials, or prepublication manuscripts if

available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)
(*c*) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.
(**3)** ***Other reporting-***
(i) ***Advertisements and promotional labeling***. The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.
(iii) ***Withdrawal of approved drug product from sale***. (*a*) The applicant shall submit on Form FDA 2657 (Drug Product Listing), within 15 working days of the withdrawal from sale of a drug product, the following information:
(*1*) The National Drug Code (NDC) number.
(*2*) The identity of the drug product by established name and by proprietary name.
(*3*) The new drug application or abbreviated application number.
(*4*) The date of withdrawal from sale. It is requested but not required that the reason for withdrawal of the drug product from sale be included with the information.
(*b*) The applicant shall submit each Form FDA-2657 to the Drug Listing Branch (HFD-334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
(*c*) Reporting under paragraph (b)(3)(iii) of this section constitutes compliance with the requirements under §207.30(a) of this chapter to report "at the discretion of the registrant when the change occurs."
(d) ***Withdrawal of approval***. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.
(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0001)
[**50 FR 7493, Feb. 22, 1985**; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 57 FR 17983, Apr. 28, 1992; 63 FR 66670, Dec. 2, 1998; 64 FR 401, Jan. 5, 1999; 65 FR 64617, **Oct. 30, 2000**]
[Effective Date Note: At 66 FR 10815, Feb. 20, 2001, the effective date for the regulation at 65 FR 64617, Oct. 30, 2000, was delayed to Apr. 30, 2001.]

Selected Sections of the Food Drug and Cosmetic Act (FDCA)

[201] Sec. 321. Definitions; generally

For the purposes of this chapter--

(b) The term **"interstate commerce"** means (1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.

(g)(1) The term **"drug"** means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph.

(k) The term **"label"** means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(m) The term **"labeling"** means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

(n) If an article is alleged to be misbranded because the labeling or advertising is **misleading**, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

(bb) The term "**knowingly**" or "**knew**" means that a person, with respect to information--

(1) has actual knowledge of the information, or

(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

(cc) For purposes of section 335a of this title, the term "high managerial agent"--

(1) means--

(A) an officer or director of a corporation or an association,

(B) a partner of a partnership, or
(C) any employee or other agent of a corporation, association, or partnership,
having duties such that the conduct of such officer, director, partner, employee, or agent may fairly be assumed to represent the policy of the corporation, association, or partnership, and
(2) includes persons having management responsibility for--
(A) submissions to the Food and Drug Administration regarding the development or approval of any drug product,
(B) production, quality assurance, or quality control of any drug product, or
(C) research and development of any drug product.

[501] Sec. 351. Adulterated drugs and devices
A drug or device shall be deemed to be adulterated--

(B) if it is a drug
and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;

[502] Sec. 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded--

(a) False or misleading label
If its labeling is false or misleading in any particular.
(f) Directions for use and warnings on label
Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this subsection, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.
(n) Prescription drug advertisements: established name; quantitative formula; side effects, contraindications, and effectiveness; prior approval; false advertising; labeling; construction of the Convention on Psychotropic Substances. In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to

be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under subsection (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with the procedure specified in section 371(e) of this title, except that (A) except in extraordinary circumstances, no regulation issued under this subsection shall require prior approval by the Secretary of the content of any advertisement, and (B) no advertisement of a prescription drug, published after the effective date of regulations issued under this subsection applicable to advertisements of prescription drugs, shall with respect to the matters specified in this subsection or covered by such regulations, be subject to the provisions of sections 52 to 57 of title 15. This subsection (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title.
[**June 25; Oct. 29, 1992**]

Review of Pantopaque's "Package Inserts"

The package insert for NDA 5-319 had the indicated dose for Pantopaque, cleared by the FDA in the NDA as **2-5cc.,** the approved intended use was for myelography, especially in the lumbar region.

The results of animal studies with Pantopaque, particularly those conducted by Steinhausen before NDA approval demonstrated the potential for severe arachnoiditis, lack of absorption, and granulomatous inflammation with neurological deficit was not adequately presented within the drug safety data either in the filed NDA, FDA communications, nor in the proposed labeling that was the result of the approved NDA.

Lafayette Pharmacal, Eastman Kodak Company, Dr. Strain, Dr. Warren, **Radiopaque Group**, University of Rochester, School of Medicine and Dentistry did not provide FDA with the complete animal experience of Dr. Steinhausen nor the negative acute clinical experience obtained from the University of Minnesota regarding difficulty with Pantopaque removal and poor myelography imaging quality. The animal and clinical safety information known by Kodak, Dr. Strain, Dr. Warren, Radiopaque Group, Rochester University Medical and Dental School and Lafayette Pharmacal was not represented within the proposed labeling submitted to FDA nor did it appear to ever have been provided adequately and honestly to the FDA within the NDA's safety information. The sponsors of the NDA, in a unique opportunity with relatively new FDCA requirements for supporting product safety, chose to focus the 1942 - 44 World War II era NDA only on favorable physician experience reports gained from treating military patients. The sponsors were able to legally manage to avoid a more rigorous requirement for short and long-

term follow-up, acute animal toxicity studies, human well-controlled clinical trials, by misrepresenting the safety outcomes of both clinical and animal experience with Pantopaque administered by intrathecal injection. As was later determined by FDA's reviewers during the Agency's review of IND 1-161 and NDA 16-377 for Pantopaque II, the firm had been allowed to avoid providing acute toxicity animal studies for support of Pantopaque safety.

Pantopaque's sponsors in 1944 simply were able to get around supplying complete and forthright animal and clinical data for Pantopaque to FDA. As a result of this successful deception, they knowlingly also did not provide adequate and truthful product information to physicians. The responsibility for providing adequate labeling resides with the "sponsor" of the product and not with the FDA. FDA, Congress and the requirements of the 1938 FDCA were designed to ensure the safety of drug products entering the US market. The laws and FDA assumes that a responsible drug sponsor will be honest and forthright in all information provided to FDA. FDA law is based on an Honor System, and it is a violation of the law for a sponsor to provide FDA with fraudulent data. The sponsor of Pantopaque intentionally provided FDA with misleading information and then created inadequate and misleading labeling for Pantopaque, promoted unapproved and off-label use of their product, and kept important safety data from the FDA, health care providers, and the public. Commencing with the initial marketing of Pantopaque, the sponsors of Pantopaque's labeling and promotion did not provide adequate warnings for safe use to physicians or the FDA and intentionally misrepresented significant preclinical and clinical experience with Pantopaque. Examples of false and misleading statements within Panopaque's 1944 labeling:

Pharmacology:

"The dosage which causes death in 24 hours in 50% of experimental animals (LD50)"
(* LD50 does not appear to have been obtained.)
"Because the medium is absorbed, there is associated a moderate toxicity."
"No toxic phenomena have been observed, however, following intrathecal injection in rabbits and dogs even when massive doses have been administered"
"In agreement with this, reports from several thousand myelograms in which 2-5 cc. of this medium has been used show that Pantopaque is well tolerated even when left in the spinal canal."
"In those cases where the bulk of the contrast medium has been removed using the technique of Kubik and Hampton*, the small amount of the material that is left is usually absorbed within 2 months".

Side Effects:

"Clinical reports indicate that the incidence and the severity of the side effects following Pantopaque myelography with aspiration of the medium is but slightly greater than with ordinary lumbar puncture."
"In 10-30 % of such cases there may be transient symptomatic reactions consisting of slight temperature elevations and increase in symptoms referable to a back condition."
"When the medium is not removed, similar transient side effects occur with a slight elevation of temperature in a greater percent of patients."

Removal of Pantopaque

"It should be possible to remove 80% to 90% of the injected Pantopaque without much difficulty."

In 1969 FDA wrote to Lafayette Pharmacal and requested that changes be made to their package inserts for Pantopaque to bring it into better compliance with prescription labeling requirements. FDA's indication for Pantopaque was still that it was intended for myelography. (* FDA indicated no claims regarding use for specific areas of the spine nor pathology detection.) FDA requested that the statement regarding absorption be deleted, and that more information be added to the adverse reactions, contraindications and precautions sections, and that the amount being commonly administered from FDA's own review of the literature should be 3 to 12 cc. FDA then requested that the new insert be submitted to FDA for agency review.

FDA requested that Lafayette add the following bullet points of information to their insert:

ADVERSE REACTIONS:

A. **Severe arachnoiditis** producing headache, fever, meningismus, pains in the back and extremities and elevations in the white blood count and the protein content of the CSF.

B. The incidence and severity of arachnoiditis are generally increased when active subarachnoid bleeding has been induced by the lumber puncture.

C. Rare instances of the development of lipoid granulomas, obstruction of the ventricular system and venous intravasation producing pulmonary emboli.

Lafayette made the following modifications to their Adverse Reactions of their physician insert, down playing the FDA's "emphasis" on the severity of the reactions in terms of the potential risk for each adverse event to occur:

(* Note all Lafayette Pharmacal Pantopaque labeling changes were required to be reviewed and approved by Eastman Kodak staff. Lafayette Pharmacal had been dealing with the FDA for the unsuccessful approval of Pantopaque II (15%) and had been conducting animal studies with Hazleton Laboratories that had demonstrated the significant long-term risks of Pantopaque I).)

Occasional severe arachnoiditis producing headache, meningismus, pains in the back and extremities and elevations in the white blood count and the protein content of the cerebrospinal fluid. The incidence and severity of arachnoiditis are generally increased when active subarachnoid bleeding has been induced by the lumbar puncture.

Rare instances of the development of lipoid granuloma, obstruction of the ventricular system and venous intravasation producing pulmonary emboli have been reported.

May 28, 1971, communication from FDA to Lafayette of the Drug Safety and Efficacy Implentation (DESI) review by the NAS-NRC indicated that the review panel recommended that the following line be deleted from Pantopaque's package insert labeling:

"The small amount of material that is left is usually absorbed within two months."

Examples of Information not included in Pantopaque's Package Insert

February 7, 1972, Lafayette Pharmacal had been informed by Dr. Scott, a physician, the hospital and the distributor Picker, that two patients at Holy Family Hospital, Altanta, GA injected with 6 cc each of Pantopaque had developed: cerebral edema, focal and grand mal seizures, hypertension, loss of bowel and bladder control, coma, aspiration pneumonia 2 hours after injection of Pantopaque with xylocaine using resusable myelography trays made by the hospital. Both patients had only ½ cc of Pantopaque retrievable after imaging.

Lafayette notified Eastman Kodak Company of the incident immediately. The hospital had informed the FDA's Atlanta District Office. The FDA's inspector inquired of Dr. Kunz *whether the problems had been adequately included within product labeling*. Dr. Kunz indicated in his note that he did not provide the inspector with an answer. The FDA inspector took samples of the product back to the FDA.

The physician, Dr. Scott, was informed by Lafayette management, who were not physicians, that 80 to 90% of the material should be able to removed without difficulty, and the physician was provided two articles. One article was regarding the risks of hospital prepared myelographic trays: British Journal of Radiology 34 (No. 405): 596- 601, 1961- **Nerve Root Radiology**, K. Bleasel. The second article, an article frequently provided by Lafayette to physicians, not specifically dealing with Pantopaque but with general intrathecal risks of residual detergents in antiseptic preparation of the skin or remaining in cleaned syringes and needles was: R.A. Smith and E.H. Conner, **Experimental Study of Intrathecal Detergents**, Anesthesiology 1962 23: 5-15.

In follow-up, February 9, 1972, a FDA inspector from Indianapolis District Office arrived at Lafayette Pharmacal to speak directly with Mr. W.S. Bucke regarding the incident at Atlanta, GA following up on the complaint that had been received at FDA. The inspector reviewed the documentation for the specific lot in question in Atlanta and inquired of Mr. Bucke whether similar complaints had been received for the lot or any other lots. Lafayette responded that there had been no other complaints to the best of their knowledge.

In terms of Lafayette's documentation of complaints received by the firm associated with acute symptoms of aseptic meningitis or chemical meningitis, in the 1970's Lafayette frequently provided physicians with articles regarding acute symptoms associated with intrathecal introduction of detergents due to processing of syringes and needles and idiosyncratic reactions with anesthetic agents. The acute meningeal symptoms being reported, also termed "chemical meningitis", were similar to the acute meningeal reactions seen within animal studies throughout the history of Pantopaque. However, Lafayette chose not to include this animal or clinical interaction information or the pertinent literature references in their physician insert nor did they appear to provide the information or the pertinent references to the FDA in 1972.

1979 Pantopaque labeling contained two literature citations: Kvernland, et al. Radiology, 72, 562-568 (1959) and Kubik and Hampton, NEJM, 224,455 (1941). There was no mention of the use of anesthetic agents or the risk of significant acute symptoms associated with the introduction of detergents. On 10/29/1979 labeling, both **Alcon Laboratories (Puerto Rico) Inc**., and **Humacao, Puerto Rico** appeared on Pantopaque physician inserts. In 1979, Alcon began to revise the physician insert for Pantopaque once again.

January 1980 Lafayette/ Alcon released their modified package insert. Either the Chynn or Cuatico myelography needle from Becton Dickenson, Rutherford, NJ. was recommended for injection of Pantopaque along with the two appropriate literature citations regarding the needles. Still the insert had no mention of the risk of aseptic or chemical meningitis associated with the introduction of detergents, or information about the acute and chronic findings that were identified in animal studies. There was also no mention within the insert of the findings at Hazelton Laboratories of the **1967-1969 acute and long-term, namely granulomatous, obliterative and/or adhesive arachnoiditis and neurological deficit,** reactions previously seen during animal studies for Pantopaque. The labeling did not add information regarding the potential for both short and long-term permanent adverse neurological manifestations, also documented within the reports of litigation that had been received by Lafayette beginning in at least the early 1960's as seen in the complaint records.

The 1980 labeling also added the need for product "filtration" of Pantopaque with a 5.0 u filter for removal of glass particles.

Misleading statements contained within the 1980 Pantopaque package insert:

(*Examples of false and misleading information of the 1943-44 insert that may persist in the 1980 insert:)

Animal Pharmacology and Animal Toxicology:

"The dosage which causes death in 24 hours in 50% of experimental animals (LD50)"
"Because the medium is absorbed, there is associated a moderate toxicity."
"No toxic phenomena have been observed, however, following intrathecal injection in rabbits and dogs even when massive doses have been administered"
"In agreement with this, reports from myelograms in which **12-30 cc.** of this medium has been used show that Pantopaque is well tolerated."

Adverse Reactions:

"Clinical reports indicate that the incidence and the severity of the side effects following Pantopaque myelography with aspiration of the medium is but slightly greater than with ordinary lumbar puncture."
"In 10-30 % of such cases there may be transient symptomatic reactions consisting of slight temperature elevations and increase in symptoms referable to a back condition."
"When the medium is not removed, similar transient side effects occur with a slight elevation of temperature in a greater percent of patients. To reduce the reactions to a

minimum, Pantopaque should be removed by aspiration after myeolography."

Occasional severe arachnoiditis producing headache, meningismus, pains in the back and extremities and elevations in the white blood count and the protein content of the cerebrospinal fluid. The incidence and severity of arachnoiditis are generally increased when active subarachnoid bleeding has been induced by the lumbar puncture.

New information regarding the needles:

Removal of Pantopaque

"It has been reported that 98% or more of the injected Pantopaque can be removed using the Chynn needle. Because of the similarity of design, the Cuatico needle should be equally effective. Occasionally it may be necessary to maneuver the medium under the tip of the aspiration cannula two or three times by tipping the table under fluoroscopic visualization before all of it can be removed and the needle withdrawn.

* Only the three prior reprints still were in the 1979 labeling. There were still no references to the information that Lafayette was supplying to physicians when asked for further information regarding Pantopaque safety and production of acute symptoms.

July 1980, the labeling was modified once again. The size of the name "**Lafayette Pharmacal**" was enlarged.

May 8, 1981, FDA received Lafayette's Pantopaque physician insert labeling for review. No other product labeling appears to have been released until 1983, and following the possible? interaction with FDA there were significant changes in the appearance and the literature citations included in the proposed insert.

March 27 1983, proposed working revision of Pantopaque labeling - changed with 9 additional new literature citations and new "acute" symptoms safety information. (*There were subsequent inter-office memos discussing the future modifications for this labeling.) The changes were as followed:

Additional information:

Dosage and Administration:

The amount of Pantopaque commonly used varies and is dependent on physician preference. However, most examinations are performed using 3 to 12 cc.

Contraindications:

An intrathecal injection should not be performed if the patient has a local or systemic infection (#2- Eng and Seligman, JAMA. 245:1456-1459 (1981).)
If bloody CSF is encountered and does not clear quickly, the possible benefits of myelogram should be considered in terms of the risk to the patient (#3 - Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976))
Precautions:
The rate of absorption of Pantopaque may vary from patient to patient.(#13- Perovitch , Radiological Evaluation of the Spinal Cord. 1:79-95 (1981))
There was the addition of literature citation #4 -Siegal, Williams and Waterman. Amer J. Neuroradiology. 3: 65-68 (1982) regarding deferment of intrathecal administration if there was a bloody lumbar tap.

*There finally appeared within this labeling revision a warning for reusable equipment. This was safety information known by Lafayette since at least 1972 that had not been included in the physician insert in prior versions. The following statements included literature citations and were as follows:

If the myelogram is performed with reusable equipment,(*Underlining added for emphasis). meticulous care should be taken to ensure the removal of the cleansing material. (#5-Denson, Joseph, Koons, Marry and Bissonnette. Anesthesiology, 18:143-144 (1957))- (*note not the same reference given by Lafayette to Dr. Scott in 1972, but certainly available long before 1983.).

A myelogram should be performed using good sterile techniques (#3- Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976)).

After thorough scrubbing the injection area, it is important to swab the area dry . Powder-free sterile gloves should be used. (#4 -Siegal, Williams and Waterman. Amer J. Neuroradiology. 3: 65-68 (1982))

Adverse Reactions now included information also relatable to the reports of acute adverse events that had been received by Lafayette within their complaint records for reported adverse reactions since the early 70's and which had not been contained within the previous physician inserts:

Adverse reactions reported following a myelogram may be due to the introduction of contrast media into the subarachnoid space, to cerebral spinal fluid leakage from the injection site, to the effects of spinal tap alone, to subarachnoid bleeding, or to the introduction of foreign material to a break in surgical technique. (#1- Shapiro, **Myelography.** 3 Ed., The Year Book Medical Publishers. (1976); #3- Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976); #7- Parker, Kane, Wiechers and Johnson, Arch of Physical Medicine & Rehabilitation, 60:220-222 (1979)).

The statement regarding clinical reports and severity of Pantopaque myelogram relatable to an ordinary lumbar puncture, now had a supportive literature citation. (#3- Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976)).

The most common side effects are headache, nausea and, rarely vomiting. (#6- Epstein. The Spine. 3rd Ed. Lea and Febiger (1969).

....vertigo, arachnoiditis, blindness, paralysis, shock and death have been reported following myelography with Pantopaque [1,3,6] (#1- Shapiro, **Myelography.** 3 Ed., The Year Book Medical Publishers. (1976); #3- Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976); #6- Epstein. The Spine. 3rd Ed. Lea and Febiger (1969).

Venous intravasation producing pulmonary emboli has been reported- *now has a reference citation-#9- Mortara and Brooks. Southern Medical Journal, 69:520-521 (1976).

Fluoroscopy and Radiology
Sometimes it is desirable to roll the patient from side to side in order to study adequately each nerve root- now had a literature citation- (#3- Taveras and Wood, Diagnostic Neuroradiology. 2nd Ed. The Williams and Wilkins Co. (1976).

April 30, 1986, there was an Alcon Laboratories receipt that showed that Alcon sent FDA a copy of the revised "**November 1985**" labeling.

Revised August 1986 Alcon labeling included the following new information:

Precautions:
Drug Interactions and/or related problems:
Glucocorticoids, intrathecal (concurrent intrathecal administration of iophendylate with intrathecal administration of glucocorticoids may increase risk of arachnoiditis.) (*Note no reference provided).
Adverse reactions:
....PANTOPAQUE should be removed by aspiration at the conclusion of the examination.

Inter-Alcon memos demonstrate that Alcon staff were in the process of revising the product labeling in 1987. However, in 1987, Alcon management determined not to purchase any further Pantopaque raw materials from Kodak Company due to the dwindling imaging market, and to slowly withdraw from the Pantopaque market.

B. Alcon's & Lafayette Pharmacal's Remarks about Pantopaque - "Labeling"

The following was an example of Alcon Laboratories's 1990's corporate responses to public inquiries regarding potential adverse effects of Pantopaque. This example provides an August 5, 1992 letter from Martha Siegal, Director, Corporate Consumer Affairs, Alcon Laboratories:

Dear

> I am responding to your letter to Alcon regarding Pantopaque.....It is obvious from your letter that the reason you now feel that many of your symptoms are related to your Pantopaque myelogram is because you watched a talk show on television that gave you the impression that Pantopaque was responsible for your problems. The show you watched presented a very biased view of the product that is totally unsupported by medical literature and medical opinions.
>
> I would strongly recommend that you discuss your condition and your suspicion, that Pantopaque may be responsible, with your current physician. I feel confident that he will advise you that the Pantopaque is not responsible. If your physician feels that your condition is attributable to Pantopaque, have him write us a letter regarding this diagnosis. We will then get in touch with your physician so we can evaluate the merits of your claim.
>
> We are very sorry that you are having medical problems. I know it is hard for you to understand why Alcon cannot discuss your problems directly with you but Pantopaque is a prescription product and as such, all of Alcon's directions and warnings are directed to the physician. The physician in turn is familiar with the individual's medical history and condition and makes decisions on the drug to use and what warning to give the patient relating to potential adverse effects of the drug. Because each patient's condition is so individual, it is important that questions regarding your condition and how it might relate to your 1981 myelogram be directed to your personnel physician.

In terms of potential litigation, Lafayette Pharmacal and Alcon Laboratories demonstrated a history of placing responsibility for initial prescription of Pantopaque and all subsequent negative effects on the **physician** (*Bold added for emphasis). who had prescribed it for use in their patient. However, this approach would have been accurate only assuming the sponsor had been forthright, as legally required by the FDCA for the FDA, with health care providers and FDA in providing all nonclinical and clinical information available regarding adequate instructions for use and warnings to allow the prescription of Pantopaque. This also would assume that the manufacturer was in full compliance with Good Manufacturing Practices (GMP) including performing adequate failure investigation, complaint handling, adverse event reporting, filing of annual reports, adverse event reports and trend analysis.

An example of Lafayette and Alcon's failure to comply with the FDCA and communicate honestly with physicians was the handling of a letter involving Dr. Robert Gross, who wrote to Lafayette Pharmacal in January 20, 1981 to request to obtain further information about the performance of Pantopaque.

> I have performed approximately five thousand Pantopaque myelographies over a period of years without any significant difficulty. However, recently I have been involved in a serious, difficult malpractice case in which the following allegations or facts have emerged for discussion:
> 1. Based primarily on an article by Chynn in 1972, it was contended that all

Pantopaque can and should be removed in all cases without exception.
2. Residual Pantopaque is a potent cause of arachnoiditis.
3. Multiple spinal punctures, if necessary, should be performed in order to insure the removal of all dyes.
4. An estimate of the amount of residual dye is the spinal canal can be made be a review of the films.
My search of the literature has failed to answer certain pertinent questions. These include:
A. The actual incidence of arachnoiditis complicating Pantopaque myelography with or without additional operative intervention.
B. The actual toxicity and safety of Pantopaque
C. The incidence of arachnoiditis when all the dye is removed or when a part is removed.
D. Pertinent statistics regarding how many Pantopaque myelograms are performed at the major centers in the U.S. in which all the dye is actually removed.

This matter is principally one of pride for me, since I am adequately covered by insurance. However, a precedent of this type, I assume would be devastating to the manufacturers and distributors of Pantopaque. I am requesting herewith that you furnish me with all the pertinent information you have available concerning the matters I have discussed in this letter.

Dr. Barry Newton, Associate Director of Research & Development, Lafayette Pharmacal, who was not a physician, and was directed to handle all medical questions and issues by Alcon Laboratories replied to Dr. Gross's requests for further information about Pantopaque in a letter of February 9, 1981:

I have included a copy of our literature references to Pantopaque for your use. I would provide the following comments on the points or questions listed in your letter:
1) Dr. Chynn's article is excellent. It provides a good deal of information about the technique for Pantopaque myelography. In a recent conversation with Dr. Chynn, he indicated that he has personally performed 4000-5000 myelograms and always removes the Pantopaque completely. He further indicated that he has never seen a problem with any of the patients that could be attributed to Pantopaque.

2) I am not familiar with any article that provides clear information on Pantopaque causing arachnoiditis.

3) I am not familiar with a publication stating "multiple spinal punctures should be performed in order to ensure the removal of all of the dye.

4) I agree that an estimate of the amount of residual dye in the spinal canal can be made by reviewing the films.

A) It is not possible for us to determine the actual incidence of arachnoiditis

> associated with myelography. Results of Pantopaque myelography do not come to my attention unless there is a problem involved. These types of calls are infrequent.
> B) The safety and toxicity of Pantopaque for use in myelography is covered through an approved NDA. Pantopaque is regarded as safe for the use intended.
> C) Information on the incidence of arachnoiditis following myelography is not available.
> D) See A and C above.
>
> Dr. Gross, to my knowledge there is no legal precedent for litigation in which Pantopaque is claimed to have caused arachnoiditis. There has never been a judgement against Pantopaque for having caused arachnoiditis.

Dr. Newton had written the above letter to Dr. Gross in 1981, yet he had also been the Lafayette employee required to respond for Lafayette Pharmacal to the September 18, 1978, letter from L. Rentz, D.O. Dr. Rentz had written:

> I am writing concerning an article in Medical World News, September 18, 1978, regarding a report by Dr. Henry L. Feffer on the profound and frequent effects of Pantopaque in causing clinically significant arachnoiditis.
>
> As you know, this opens the doors of future malpractice litigation. Certainly myelography is one of the most common causes of legal action at the present time and your agent is the only one clinically acceptable. I would greatly appreciate detailed copies of the papers referred to this in this news report.

Dr. Newton's October 11, 1978 response as Lafayette's Product Complaint Coordinator to Dr. Rentz was as followed::

> Your letter of September 19, 1978 has been forwarded to me. Medical World News is not one of the journals that we receive and therefore I have not seen a copy of the article by Dr. H.L.Feffer. If you would be so kind as to send me a copy of this article to my attention, I would appreciate it.

Dr. Renz subsequently did send a copy of the article to Dr. Newton. The article was named: **Arachnoiditis Risk after Myelography.** The article included official comments by an unnamed Lafayette spokesman regarding the Lafayette response to the contents of the article. It was authored by a team of physicians from George Washington University. The authors stated:

> Of the estimated 400,000 myelograms done yearly in the U.S. at least one fourth of the patients will probably develop iophenydylate arachnoiditis on the basis of our four studies, ...moreover, patients who have had two or more studies with the iodinated contrast medium stand a 50% chance of developing iatrogenic arachnoiditis....In the past we have questioned whether our poor results were due to surgery, the original back-pain complaint, or the oily based contrast agent. Now we know.

> A spokesman for Lafayette Pharmacal, which markets iophendylate as Pantopaque demurs: "There is no evidence that supports the authors' conclusions. They describe no method for analyzing the data that make a possible logical conclusion about the factors that influence arachnoiditis. Regression analysis demonstrates no positive relationships between the number of Pantoaque myelograms and the occurrence of arachnoiditis nor between the number of operations and the occurrence of arachnoiditis.
>
> In their text, Diagnostic Neuroradiology (2nd Edit, p.1136) Taveras and Wood state: Myelography with Pantoaque is followed by surprisingly few side reactions aside from those usually associated with lumbar punctures.

The Washington researchers along with Dr. Haughton, Medical College of Wisconsin in Milwaukee said that their closer scrutiny of their facilities' iophendylate procedures demonstrated that there was a higher incidence of arachnoiditis than initially had been thought. Dr. Feffer also partly blamed a general imaging policy for performing myelograms without adequate justification in terms of a when viewed as a strict risk-benefit analysis since myelograms produced scarring and adhesions in the arachnoid. He blamed imprecise technique such as epidural injection, significant dye retention, and emulsification of the contrast medium by bloody admixture as increasing the potential risks. The authors concluded their article by the following statement:

> Animal studies confirm the "devastating effect of iophendylate on the myelin sheath and nerve cells as well as the meninges and nerve roots." says Dr. Feffer. Wisconsin's Dr. Haughton, who has done studies comparing iophendylate and metrizamide in primates, concludes water-soluble material causes fewer side effects."

October 3, 1978, Dr. B. Newton, now as "Director of Organic R&D", responded to a letter received from Dr. George Wilson:

> After reviewing my files on Pantopaque publications, I have been unable to locate any publication dealing with meningitis type of reactions to Pantopaque. There are however, references made to the possibility of arachnoiditis from Pantopaque retained in the S/A space. I have also been unable to locate any reference in our files dealing with the possible contamination of material with enterobacter agglomeranes. I have discussed the possibility of changing our packaging insert to recommend sterilization of the outside of the ampul just prior to use. We are in the process of evaluating a package revision and your suggestion will be very closely evaluated as a simultaneous change.

August 13, 1979 Dr. Newton wrote another reply letter, now to Mr. Boyd, President, Rebco Incorporated, a distributor of Pantopaque, regarding a reported adverse reaction that had been reported to Mr. Boyd by one of his clients:

> Your letter to C.W. Griggs dated August 3, 1979 has been forwarded to me. Mr

Griggs retired from Lafayette Pharmacal earlier this year.

In response to your letter inquiring about recent reports on problems with Pantopaque, we have not observed any change in the incidence of type of inquiries received on the use of Pantopaque. There has been one inquiry involving Pantopaque from lot number 121518. A field a sample of that material was received at Lafayette Pharmacal and that sample met U.S. Pharmacopeia requirements and was sterile.

If it would be of service to you I would be happy to contact your customer to discuss this matter with them. If they have any of the lot of Pantopaque still at their hospital I would request a sample be sent to us for analysis.

Another example of Lafayette communication was recorded in an inter-office memo that occurred between Lafayette Pharmacal's Dr. Newton, and a concerned physician father, a Richmond, VA allergy specialist, regarding the safety of his daughter. The physician was asking questions similar to Dr. Gross's questions of 1981:

Dr_____ wanted to know if there was a relationship between retained Pantopaque and arachnoiditis- What would be the effect of a couple of droplets?

I told him about Taveus and Wood- Pantopaque gives reactions no different from a spinal tap- **I told him retained Pantopaque should present not problem**.(* Bold for emphasis). I told him it was our experience that should Pantopaque be left in the CSF microphages (sic) would form and gradually the material would be eliminated. We had not seen inflammatory responses in animals-
He asked if it would be possible to aspirate two droplets of Pantopaque-
I asked if it was mobile- No-
My statement was that it would be difficult- it would depend on the skill of the person making the tap to place the tip of the needle near the material.

I told him about the practice of leaving Pantopaque in the SA space in England (years past). I also related to him about radiologists frequently seeing retained Pantopaque without the patient being aware of its presence.

Dr._____ inquired about suggested therapy for arachnoiditis-
I told him there were reports in the literature about the use of steroids-
After several minutes of discussion, it was discovered that Dr._____ daughter was the patient involved- She was 25 years old-had three operations-was in a great deal of pain- Some other doctor was recommending metrizamide and he wanted to know my opinion.-I made no recommendation other than suggesting he could read the literature on metrizamide.
I told Dr._____ that a bloody tap at the time of the myelogram had been implicated in arachnoiditis.
Dr._____ indicated that his daughter was rather excitable and was getting upset about the condition.

I took his address but made no commitment to him about sending literature- Since he is not her personal doctor, I do not feel we should send him literature.

VII. Manufacturers Involved in the Production and Marketing of Pantopaque

A. Eastman Kodak Company

Eastman Kodak Company has a history in photography and radiology imaging that goes back to the turn of the century and the original need for radiologic products. In terms of Pantopaque, in 1938, Distillation Products Incorporated (DPI) began manufacturing vitamin concentrates for Kodak and in 1948, Kodak bought out General Mills' interest in DPI. In 1942, Kodak's Rochester plants were awarded the Army-Navy "E" for high achievement in the production of equipment and films for support of the war effort. During 1947, Kodak began the first commercial production of synthetic Vitamin A at DPI which continued until 1973. 1977 Arkansas Eastman Company, the newest member of the Eastman Chemicals Division, began commercial production of organic chemicals, and 1978, Eastman Chemicals Division introduced Eastman KODAPAK thermoplastic polyester for use in manufacturing beverage bottles. Therefore, Kodak had interests and operations outside film production.

By 2001, Eastman Kodak Company has remained a publicly traded company, employing 80,650 and still headquartered in Rochester, NY. Its subsidiary is Kodak Health Imaging Services. Kodak is not identified as a producer of injectable imaging contrast agents. From the documentation I have reviewed, its facilities last provided Alcon Laboratories with ethyl iodophenylundecylate for production of Pantopaque in 1987. Kodak owned the trademark for Pantopaque while Alcon Laboratories held the NDA.

B. Alcon Laboratories, Inc.

Alcon Laboratories was started as a pharmacy in Fort Worth, Texas, Alcon Prescription Laboratory, in 1945 by two pharmacists, Robert Alexander and William Conner. The initial product they produced and marketed were injectable vitamins. Alcon Laboratories incorporated in 1947, to raise capital and begin manufacturing and promoting sterile ophthalmic solutions. Throughout the 1970's Alcon's research and development has focused their efforts primarily towards development of ophthalmic products. In 1977 Alcon Laboratories was acquired by Nestle, the world's largest food company, which is headquartered in Switzerland. Following acquisition by Nestle, Alcon launched multiple new manufacturing plants in the United States, Belgium, Spain, Mexico, Brazil, Puerto Rico, and France with an expansion of Alcon's areas of research and product development, including Pantopaque.

In 1972, Ed Schollmaier succeeded William Conner, founder and first Alcon President, as the second President of Alcon. He was replaced in 1997 by Tim Sear. Today Alcon Laboratories represents a $2.55 billion global pharmaceutical company that specializes in the development, manufacture, and marketing of ophthalmic surgical, vison care and otic products.
(*Also in 1977, besides their acquisition by Nestle, Alcon Laboratories acquired Lafayette Pharmacal, Inc. and the product Pantopaque.)

In addition to drug products, Alcon Laboratories has had 57 medical device 510(k)s cleared for marketing and approval of 16 Premarketing Approval Applications (PMAs) by FDA, CDRH.

Alcon Laboratories and FDA

Besides the Agency's visit in 1989 of the Alcon Humacao, PR facility, FDA visited Alcon Humacao, Puerto Rico in September 4 & 5, 1991 to inspect the facility's Purified Water System and involvement with a local gastroenteritis outbreak. There had been a prior limited inspection by FDA June 1991 regarding approval of Alcon's PMA by FDA's CDRH. The FDA inspection revealed no problems related to the gastroenteritis outbreak that had been experienced within the area of Humacao, P.R. , and there were no problems identified with the water quality. However, FDA issued a FD- 483 to Alcon management reporting they had found two items regarding the failure to have an IQ (Installation Qualification) program for water processing systems validated and for the firm not generating IQ reports for water systems modifications. The agency viewed these as important issues since the company facility functioned primarily as an ophthalmic solutions and production plant.

May 15, 1991, FDA conducted a limited inspection of the Ft Worth, TX Alcon facility to cover the features of the TRP (tamper resistant proof) on Alcon's Contact Lens Cleaning Solution . The inspection request followed the Agency's receipt of official samples collected Sept 90 and again in March 91 that failed to document Tamper Resistant Proof (TRP) features on private label CLC Solutions. At the time of sampling, Alcon had not placed appropriate TRP features on a vast array of private label 12 fl oz CLC Saline Solutions. Alcon's own OTC products all contained the appropriate TRP features. After a meeting with the FDA inspector, Alcon's management promised to incorporate distinctive plastic shrinkband feature onto the bottle necks of the private label products.

March 1, 1994 FDA issued Alcon a Form- 483 following the agency's inspection of the Alcon Puerto Rico facility from January 19 through March 1994. Regarding, earlier agency interaction with Alcon, the agency's report began that the firm had been the subject of various inspections during the last year. The most comprehensive inspection had been made during March 27- June 14, 1993 and had covered the ophthalmic and device operations. In the ophthalmic operations, the inspection disclosed repeated and new significant GMP deficiencies which included: lack of full manufacturing process validation for all ophthalmic products; leaky tanks which contributed to the contamination of two media fills; failure to evaluate the effect of preservation when conducting re-testing of products that had failed initial sterility testing; stability failures within the expiration period; incorrect stability data had been submitted to the FDA in the Annual Report; non-validated process of adding additional water and /or active ingredient to a sterile product found to be over-potent or sub-potent.

In the medical device operations, the Agency's inspection revealed the following: the firm was using water with rust residues (iron, chromium, nickel) in the manufacture of Viscoat; bulk material Avitene was not tested for pyrogen (LAL test); erroneous calculations of the LAL lead to release of product with invalid results.

In addition, FDA's Sterile Drugs Branch, Division of Manufacturing and Product Quality, had recommended a mass seizure of Alcon's sterile ophthalmic solution and suspension drug products manufactured at Alcon's Humacao, P.R.plant, and in Alcon's possession at four different warehouses. Also as a result of the inspection, FDA withheld approval of 2 Alcon ANDA's and 3 NDA's under review at the Agency. However, with FDA's permission, Alcon agreed to consolidate the violative products that were the subject of the Agency's seizure recommendation to their Fort Worth Headquarters and Alcon then destroyed the #1.2 million products in Fort Worth under FDA supervision. Subsequently, FDA agreed to withdraw its seizure recommendation.

June 8, 1993, FDA returned to the Alcon Houston, TX facility to conduct a limited inspection to determine the current disposition of ophthalmic products produced between 04/01/1992 and 09/30/1992 at the Alcon plant in Puerto Rico and considered by FDA to be adulterated. An agreement was made between Alcon and FDA to destroy all product since Alcon refused to recall the product. Mrs Bulaw of Alcon had already been aware of the problem with their sterile ophthalmic products prior to FDA's arrival and handed FDA's inspector a June 1, 1993 Alcon memo indicating that the remaining products which were considered adulterated by FDA would be consolidated at the Ft. Worth, TX facility where they would be destroyed by Alcon personnel.

A limited Agency inspection was made July 8-12, 1993, as a follow up to the earlier June inspection and FDA found continued failures related to the holding tanks, and having a SOP with specific instruction to be followed if tanks leak during the holding and filling operations.

November 2, 3, 5, 1993, FDA conducted a device GMP inspection and uncovered further deviations including a failure to submit mandatory **Medical Device Reports** (MDRs) for complaints that had been received that were relatable to potential serious patient injury.

The 1994 inspection of Humacao, PR Alcon continued to find significant manufacturing deviations regarding new NDA products and GMP deficiencies that significantly affected their drug production in general at the plant. Pre-approval samples were not collected because of the firm's decision to withdraw the Puerto Rico manufacturing site from the NDAs for four of the products in order to accelerate the Agency's approval process. Documentary samples were collected to document interstate commerce of drug products from two different profiles that may be affected by the firm's failure to maintain an adequate stability area under controlled conditions. In 1993, Ms. Maria Santiago was designated the Technical Assistant to the General Manager leaving vacant the QA Director position at the time of inspection.

Manufacturing facilities at the Humacao, Puerto Rico site consisted of three separate buildings that were identified as follows: Avicon Plant, Ophthalmic Plant, and Vision Care Plant. The Avicon manufacturing building was dedicated to the packaging of microfibrillar collagen hemostat and to the manufacture of ophthalmic contact lens care products. The Ophthalmic building was used to manufacture sterile ophthalmic solutions, suspension, contact lens care solutions and surgical solutions. Vision Care Plant underwent recent expansion for production of NDA products.

Alcon's Warning Letters (1993-2000)

1. June 6, 1993 Alcon, Fort Worth, Texas, was issued a Warning Letter by FDA that Alcon was manufacturing as a prescription ophthalmic drug for relief of signs of allergic conjunctivitis in violation of the FDCA. An FDA Federal Register on October 1, 1992 had stated that products containing Antazoline Phosphate or Naphazoline Hydrochloride in combination with other ingredients or any other products containing an antihistamine in combination with a vasoconstrictor for such use could no longer be marketed without an approved NDA. Therefore, FDA cited Alcon as in violation of the FDCA and considered the drug a "New Drug". The product could not be legally delivered into U.S. interstate commerce without FDA's prior approval of an NDA.

> It is your responsibility to ensure that all drug products marketed by your firm comply with the Act and all regulations promulgated thereunder.

2. July 30, 1993, Alcon Laboratories, Fort Worth were issued a Warning Letter following FDA's inspection of Alcon Surgical, Inc. located in Huntington, West Virginia. The Agency's inspector found deviations from Good Manufacturing Practices (GMP) in Alcon's manufacture of implanted intraocular lenses. Manufacturing specifications, processing procedures, and controls were found to be inadequate. The Quality Assurance programs were inadequate, failure to conduct adequate failure investigations, failure to conduct adequate critical device inspection, following FDA's limited inspection of the facilities.

3. December 14, 1995, FDA sent a Warning Letter to Mr. E. Schollmaier, President and CEO of Alcon Laboratories, Inc for problems that continued to be identified at the Huntington, West Virginia Alcon facility following FDA's inspection conducted November 14-28, 1995 for the manufacturer of intraocular lenses. The same problems were identified as during the 1993 inspection of the facility.

4. March 20, 1998 FDA issued a Warning Letter to R. Gural, Ph.D., VP, Regulatory Affairs regarding Alcon's broadcasting of product advertisement for Patanol 0.1% solution. FDA's DDMAC had determined that the advertisement was in violation of the FDCA in that the advertisment (promotion) was misleading. Alcon stated in the advertisement that "few people may experience side effects, like headache." FDA's DDMAC (Division of Drug Marketing and Communications) did not consider that an adequate representation of the risk information. In a telephone conversation between FDA and Mr. Gural of Alcon, he stated that Alcon would stop airing the ad. However, in a follow-up conversation Mr. Bural proposed that Alcon replace the subject advertisement with a voice-over. That was not considered acceptable by FDA.

5. August 11, 1998 FDA sent a Warning Letter to Mr. Tim Sear, President and CEO of Alcon for the Huntington, West Virginia facility. FDA conducted their inspection May 2 to June 10, 1998. Again the FDA found their manufacture of intraocular lenses at the facility in violation of the law in that the devices are misbranded due to Alcon's failing to file **MDRs** for reports received of their implanted lenses (critical devices) failing and producing serious injury in patients.

6. November 19, 1998, Alcon's Scott Krueger, Director of Regulatory Affairs, received a

Warning Letter from FDA's DDMAC regarding the firm's marketing and promotion of TobraDex. Alcon was promoting the product for both optic and otic use when it had been cleared for only optic use. Alcon was also promoting the product at the American Association of Otolaryngolgoy convention in September 14-16, 1998, which FDA considered a promotion for off-label use.

7. January 5, 1999 Alcon Laboratories, Scott Kruger received a Warning Letter from DDMAC for Alcon's promotion of Azopt. The promotion of the product was not in keeping with the clearance for the product, lacked fair balance, and were misleading.

8. January 14, 1999, Tim Sear, President and CEO of Alcon Laboratories received a Warning Letter for his firm's promotion of Alcon's Acrysof Intraocular Lenses. FDA objected to promotions in marketing that had been sent to physicians by Alcon that specifically stated:

> We at Alcon Laboratories are very excited and pleased that the FDA[sic] has given us permission to change our labeling on our Acrysof Lens Package insert. We have been able to demonstrate over a three-year period. [sic] scientifically that Acrysof lenses do not reduce posterior capsular opacification."
>
> We have anecdotally discussed this, however the enclosed study and package insert demonstrates [sic] this outcome.....This is a milestone for Alcon as this is the very first claim that any manufacturer can makes towards PCO.

FDA found these statements objectionable, in violation of the FDCA and Alcon's actions had made the device misbranded and adulterated. The lenses were misbranded because the company had not submitted a notice or any other data to FDA that could support the new claims made in the promotional information. FDA considered the device adulterated because the Acrysof Lens were a class III device that would require an approved PMA for the product claims. FDA's latter stated:

> We have been advised by CDRH's Office of Device Evaluation (ODE) that in Alcon's discussions with the agency about the approval of additional claims for the Acrysof lens labeling, ODE explicitly advised Alcon that the additions were limited to claims regarding the utility of the lens in reducing lens epithelial cells. ODE advised the company that claim for reduction or posterior capsule opacification (PCO) exceeded what the company had studied and that FDA would want any claim of reduction in PCO to be evaluated by the Ophthalmic Devices Panel. The company committed to making claims only for the reduction in less epithelial cells.
>
> ...In addition to the violations described above, Alcon has made other violative promotional claims. On October 28, 1998, our office issued a latter to Alcon discussing violative claims on the company's website....The company has, to date, failed to respond to that letter and the website continues to make the inappropriate claims. Please include in your response to the warning letter a discussion of how you intend to address the issues raised in the October 28 letter.

9. February 23, 1999, Mr. Scott Kruger, Director, Regulatory Affairs Alcon, received a Warning Letter form FDA's DDMAC regarding the firms false and misleading marketing of Betoptic S in violation of the FDCA. The agency had no record of Alcon's submission of this marketing campaign for the agency's review and the claims implied clearance for an unapproved new use. Namely, the promotion implied the product was cleared to protect patients from visual field-diminishing effects of glaucoma. Whereas, the product had been indicated for lowering intraocular pressure in patients with chronic open-angle glaucoma and ocular hypertension. The agency's letter stated:

> DDMAC is especially concerned about this promotional issue because DDMAC has previously inquired about Alcon's alleged promotion of betaxolol in connection with ocular blood flow and preservation of visual field. On February 15,1994, Alcon responded to an inquiry from DDMAC regarding this alleged promotion, and stated that in response to DDMAC's request, Alcon was "taking measures to ensure that there will be no further discussion of the effect of betaxolol on visual field or blood flow...in materials used by Alcon sales representatives. However, it appears from the dissemination of the above advertisement that Alcon is promoting betaxolol in connection with the preservation of the visual field.

10. March 15, 1999, Mr. Kruger received another Warning Letter from FDA's DDMAC regarding Alcon's promotion for unapproved use and unsupported clinical claims for the product Ciloxan. Alcon was promoting the product for prophylaxis for ophthalmic surgery when it had been approved only for the treatment of infections for susceptible strains of organisms- not prophylaxis.

11. March 16, 1999, Mr. Kruger was went a Warning Letter from FDA's DDMAC regarding the firm's inadequate response to the agency's Warning Letter for March 19, 1999 regarding the promotion of TobraDex. The agency considered the advertising as not providing a fair balance, and still in violation of the FDCA.

12. June 12, 2000, Mr Kruger received another Warning Letter from DDMAC regarding the promotion of Ciloxan. The agency indicated that the firm continued to make misleading claims of effectiveness, make promotions that lack fair balance and provide misleading presentations of in vitro data.

13. November 17, 2000 Mr. Sear, President of Alcon received a Warning Letter from FDA following the agency's inspection of the Fort Worth manufacturing facility that was conducted October 12-27, 2000. FDA found the firm in serious deviations from the Current Good Manufacturing Practices for Finished Pharmaceuticals and the Quality System Regulations. These deviations caused Alcon drug products and medical devices manufactured at the site to be adulterated and in violation of the FDCA.

C. Lafayette Pharmaceutical Inc.

Lafayette Pharmaceuticals, Inc continues to be based in Lafayette, Indiana, however, its present

parent company is listed as Inovision, Solon, Ohio. Mr. R.A. Sharp continues to be the head of Regulatory Affairs for Lafayette Pharmaceuticals, Inc., as well as for Lafayette Pharmaceuticals Incorporated based in Yorba Linda, Ca. Another subsidiary of Inovision is also Nuclear Associates, Carle Place, NY. The Yorba Linda "Lafayette" firm uses the tradenames: "Micropaque", Tridate, and Energel. Lafayette Pharmaceuticals based in Lafayette, IN uses the tradenames: "Aircon", "Anatrast", "Baricon", "Barocat", Barosperse, Cheetah, Energel, Entrocel, Liquid Barosperse, Sparkles, Tomocat, "Tonopaque", Tridrate. Nuclear Associates, which has a revenue of $10-25 million annually, produces primarily imaging medical devices. Lafayette Pharmaceutical, Inc is a manufacturer of both drugs and medical devices. Lafayette Pharmaceuticals has had 5 510(k)s for marketing cleared by FDA from 1986-1993.

Lafayette Pharmaceutical's Medical Device Reports (MDRs)- Mandatory Reporting

Pre1996 and the beginning of the MAUDE MDR database, Lafayette had filed a total of 2 MDRs for receipt of reports of complaints received regarding the performance and/or safety of their medical devices during the period 1984-1996. Both MDRs were filed in 1992 for disposable pre-filled barium enema kits, potentially both related to an "allergic" reaction.

One MDR, February 28, 1992, identified incorrectly as a malfunction, rather than a serious injury, the patient developed allergic reaction and was subsequently determined to be allergic to the latex in the barium enema tip. The second MDR, March 28, 1992, also incorrectly identified as a malfunction, occurred also during a barium enema, when a patient went into respiratory arrest (coded), and recovered.

Since 1996, Lafayette Pharmaceuticals, Inc. has filed only a single MDR in 1997. The report was for the Barosperse Enema Kit and that the firm had been informed that the patient suffered a ruptured colon during barium enema.

VIII. OPINIONS

1. Lafayette Pharmacal, Inc., and Alcon Laboratories, Inc. failed to behave as reasonable U.S. manufacturers when they pursued actions intended to mislead and conceal important drug safety and performance information from the Food and Drug Administration (FDA), medical community and the U.S. public. Lafayette Pharmacal and Alcon Laboratories, Inc. disregarded the role of the Food Drug and Administration for protecting public safety when they failed to provide the Agency with adequate labeling, warnings, truthful federal submissions, and violated Good Manufacturing Practices by not conducting adequate failure investigation and filing timely adverse event reports for serious patient injuries. Despite the firms' awareness of a significant body of animal and human data that demonstrated Pantopaque could be toxic and associated with an unreasonable danger to health when used as intended, the firms continued to market it to physicians for patient imaging. Such irresponsible and callous actions based on the pursuit of financial

gain demonstrated a total disregard for U.S. public health.

Complete and accurate animal and clinical safety and toxicity information known by Lafayette Pharmacal, Inc., prior to 1944 and later by Alcon Laboratories, in 1978, regarding the true risks of Pantopaque were not honestly and accurately provided to FDA within federal submissions. The data was not presented to FDA, the medical community, nor the public within adequate product labels, promotions or communications by either Alcon Laboratories or Lafayette Pharmacal.

The initial Pantopaque New Drug Application, NDA 5-319, was approved by an FDA that was involved in World War II under newly evolving requirements of the 1938 FDCA. Pantopaque's approval came as the result of the firm's misrepresentation of animal safety data, selective omission of unfavorable human experience data, reliance on reports of positive physician experience from research conducted on military patients.

Lafayette Pharmacal, Inc., was successfully able to capitalize upon unique conditions that allowed Pantopaque to enter a US imaging market without supplying valid "safety" data in their NDA. The firm was provided a marketing opportunity that allowed them to quickly reach and remain on the U.S. imaging market through the 1990s and the 1978 advent of water-soluble and imaging agents.

After passage of the 1962 Drug Amendments to the Food Drug and Cosmetic Act, and NAS/NRC DESI retrospective review of published medical literature to support Pantopaque's imaging "efficacy", the drug was allowed to remain on the US market. Subsequently, FDA and NAS/NRC requested changes in the physician insert that would better and more accurately inform the user of :1) the need to remove the material from the spinal canal post imaging, and 2) the potential for Pantopaque to be associated with significant serious permanent neurological effects.

During 1963, IND1-161 NDA 16-377 were filed by Lafayette to obtain FDA's approval of a new generation of Pantopaque or Pantopaque II. FDA's approval of NDA16-377 and IND1-161 for future marketing of Pantopaque II necessitated, among many other requirements, that the firm provide FDA with adequate animal toxicity safety data to assure human safety. Adequate animal toxicity safety data that had been submitted by the firm in NDA5-319, would have been allowed to be used for support of human safety for the Pantopaque II IND and NDA. However, NDA5-319 animal safety data was found to be inadequate by FDA reviewers for support of human safety.

Filing of an NDA now required a drug sponsor to obtain an IND exemption to allow legal distribution of an investigational drug within the US for the purpose of conductance of a clinical investigation. The obtaining of an IND brought new requirements for accounting for the distribution of an investigational drug product, for facilitating the gathering of valid scientific evidence to support safety and efficacy, obtaining oversight by IRB, and obtaining adequate informed consent. The "IND" mechanism required FDA's prior approval of a clinical trial design. FDA as a regulatory agency was evolving from the Agency that Lafayette Pharmacal had dealt with amidst the turmoil of 1944.

The Pantopaque II marketing applications were subsequently withdrawn from FDA by the firm June 25, 1969. Also in 1969, the sponsors had received the final conclusions of animal toxicity studies conducted by Hazelton Laboratories that had involved toxicity studies for both the investigational and the approved Pantopaque products. When the IND and NDA was withdrawn, the unfavorable animal toxicity data for both the investigational and the approved Pantopaque products was not conveyed to FDA, despite the Agency's specific requests that the firm be forthright and honest about Pantopaque product information. Rather, FDA was told that the NDA was withdrawn by Lafayette after learning that Pantopaque II was no more "effective" than Pantopaque I.

After the initial twenty years on the US market, the recommended maximum administered dose for Pantopaque by Lafayette had been escalated from 5 ccs of the NDA, to a labeling maximum dose of 9ccs in 1953 and, following DESI's medical literature search, a maximum dose of 12 ccs. A reasonable appearing increase for a product if it were indeed "safe". However, the greater the total dose of Pantopaque injected by the physician, the greater the potential amount left remaining permanently within the patient's spinal canal and the increased permanent disabling risks. After almost 40 years on the US market, in 1980 labeling, the safe maximum tolerated dose implied for Pantopaque in Lafayette labeling was suggested to be as high as 30 ccs. Each increase in total patient dose of Pantopaque for myelography by Lafayette Pharmacal, moved the patient and the product unknowingly further away from NDA5-319.

FDA's 1944 Pantopaque approval and 1969 Pantopaque II withdrawal interactions were predicated on the assumption that FDA was dealing with reasonable, responsible and honest US sponsor of marketing applications, in full compliance with the requirements of the Food Drug and Cosmetic Act (FDCA). A reasonable U.S. manufacturer would not seek to violate the FDCA, nor would they perform a prohibited act and market a product that they know is dangerous. A reasonable U.S. manufacturer would not misrepresent product safety and performance to FDA, the U.S. medical community, and the U.S. public. Lafayette Pharmacal and Alcon Laboartories, Inc. had become aware, long before the product's removal from the US market which Alcon Laboratories began in 1987, that injection of Pantopaque into the human subarachnoid space was potentially dangerous, toxic, and NOT safe.

It is my opinion to a reasonable degree of medical certainty and based on my training and experience, that Lafayette Pharmacal, Inc., and Alcon Laboratories, Inc. failed to behave as responsible US manufacturers when they :

a) conspired not to supply complete and forthright animal and clinical data regarding the risks of injection of Pantopaque into the subarachnoid space for myelography to FDA and the medical community;
b) failed to provide adequate and truthful information to FDA, the medical community, and the U.S. public in official federal documents, labeling, product promotions, written and oral communications while downplaying the severity of adverse events and risks;
c) knowingly marketed a product to the U.S. public through promoting prescription by physicians by not providing physicians with adequate information regarding potential risks and benefits;

d) knowingly marketed a product that could be dangerous to physicians when they were aware that Pantopaque had been toxic to animals and humans when injected into the subarachnoid space and associated with granulomatous meningitis; severe progressive obliterative arachnoiditis; adhesive arachnoiditis; paralysis; seizures; bladder and bowel dysfunction; coma; and even death;
d) placed corporate profits from sales of Pantopaque over legal responsibilities and obligations to ensure U.S. public and product safety.

Such irresponsible and dangerous actions by Lafayette Pharmacal and Alcon Laboratories prior to 1983 directly contributed to the pain and suffering of the U.S. public exposed to Pantopaque and directly contributed to the US healthcare burden.

2. Lafayette Pharmacal and Alcon Laboratories through 1983 demonstrated a total disregard for the role of FDA, physicians and U.S. manufacturers to ensure U.S. public safety by providing Pantopaque with labeling that implied to both FDA and the user that adverse effects reported for Pantopaque were negligible, transient, short term and limited. Such negligent actions by Lafayette Pharmacal and Alcon Laboratories to downplay the severity of the risks on injected Pantopaque prior to 1983 directly contributed to the permanent Pantopaque-related spinal injuries produced by Pantopaque injection in the U.S. population and added to the long term financial burdens of the US healthcare system.

Pantopaque's labeling was misleading, false and failed to convey the severity of both the immediate and chronic dangers associated with injection of Pantopaque into the human subarachnoid space. Misleading and inadequate labeling did not provide the prescribing physician with valid and honest information regarding true product risks in terms of potential imaging benefit. Without such truthful and accurate product information, physicians were unable to make valid risk versus benefit determination regarding the prescription of Pantopaque for imaging of patients.

Lafayette Pharmacal and Alcon Laboratories labeling of Pantopaque, through just a review of medical literature, animal studies and adverse event reports prior to 1983 should have, at a minimum, included the following information in the physician insert under "WARNING"s, "PRECAUTION"s, and/or ADVERSE REACTIONS:

1. Pantopaque is not water-soluble and remains primarily unabsorbed in the body.

2. Pantopaque histologically has been shown to trigger a severe granulomatous foreign body inflammatory reaction.

3. Injection of Pantopaque into the subarachnoid space for myelography has been **acutely** associated with producing symptoms of aseptic and chemical meningitis; fever; shock; respiratory arrest; coma and death.

4.Pantopaque myeolography has been **chronically** associated with severe chronic, adhesive and obliterative arachnoiditis; progressive neurological deficit; paralysis; focal and grand mal seizures; blindness; cauda equina syndrome; obstructive hydrocephalus; chronic pain; shock; coma; and death.

5. Physicians have reported inability to remove all injected Pantopaque by lumbar puncture and fluoroscopy following myeolography even by the recommended procedure of Kubik and Hampton, and using Chynn and/or Cuatico needles. Therefore, the potential imaging benefits of Pantopaque should be considered in terms of potential permanent risks.

6. Injection of Pantopaque carries both significant and severe acute and long term risks for the patient beyond the risks of routine lumbar puncture.

7. Human hypersensitization studies with Pantopaque have never been conducted.

Points 1-7 listed above were not contained within Pantopaque's package inserts through 1983 and therefore, the product labeling was misleading, false, and inadequate to ensure patient safety.

In terms of findings of animal testing data provided to both FDA and users, the labeling was also false, misleading and dangerous to the public's health when the following points 1-5 were not accurately described:

1. Acute toxicity studies with intrathecal Pantopaque in dogs, produced symptoms, not associated with a dose effect, of neurological deficit with loss of motor control in the lower extremities; aseptic meningitis; fever; and connective tissue lesions in the area of the injection site.

2. Chronic toxicity studies with retained intrathecal Pantopaque in dogs, produced symptoms, associated with a dose effect, of variable degrees of severe granulomatous meningitis involving the brain and spinal cord in areas where the material tended to localize; severe fibrosis of the meninges and arachnoid surrounding encysted retained Pantopaque; subacute and chronic inflammation; nerve root damage; and cerebral hemorrhage.

3. Pantopaque was not demonstrated to be absorbed in animal studies following intrathecal, intraalveolar, or intraperitoneal routes of administration.

4. In animals studies, not associated with a dose effect, Pantopaque histologically triggered significant acute and chronic granulomatous foreign body inflammation surrounding nonstaining vacuoles and cysts of retained Pantopaque, with multinucleated giant cells, fibrobasts, lymphocytes, plasma cells and fibrosis.

5. LD50 studies were not conducted for Pantopaque, and lethal dose was estimated.

It is also my opinion, within a reasonable degree of medical certainty, and based upon my training and experience, that such negligent actions by Lafayette Pharmacal and Alcon Laboratories prior to 1983 directly contributed to the chronic Pantopaque-related spinal injuries that have been reported within the U.S. population.

3. When Alcon Laboratories, Inc. acquired Lafayette Pharmacal, Inc. January 1978, their corporate management was aware that inadequate safety and efficacy data and animal safety testing had been conducted by Lafayette Pharmacal and that the product Pantopaque was being marketed in violation of the FDCA. Yet, Alcon Laboratories took no corporate actions to comply with the requirements of the FDCA nor to protect public safety.

The inadequacy of Pantopaque safety studies were pointed out to Lafayette's management by Alcon Laboratories when it acquired Lafayette in 1978. Alcon Laboratories management were aware that the safety data for Pantopaque would not be able to support marketing of Pantopaque through clinical performance comparisons to a competitor's product using well-controlled studies since well-controlled studies with Pantopaque had never been conducted.. However, Alcon Laboratories, Inc. took no steps to see that well-controlled clinical trials and adequate safety trials were conducted with Pantopaque, took no steps to bring Pantopaque into compliance with FDCA, nor took steps to assure adequate failure investigation or timely adverse event reporting. Instead, Alcon Laboratories elected to continue to profit from Pantopaque's marketing, despite inadequate safety and clinical trials, and labeling showing a total disregard for U.S. public safety.

It is also my opinion, within a reasonable degree of medical certainty, and based on my training and experience, that such negligent actions by Lafayette Pharmacal and Alcon Laboratories prior to 1983 directly contributed to the chronic Pantopaque-related spinal injuries reported within the U.S. population.

4. Beginning in the 1940's and extending through Alcon Laboratories's 1978 acquisition of Lafayette Pharmacal, based on the adverse clinical and animal data that was available to Lafayette Pharmacal and Alcon Laboratories regarding "safety" of iophendylate, Pantopaque's labeling remained inadequate, false and misleading for physicians, FDA, and the U.S. public. Pantopaque's labeling specifically failed to provide adequate warnings to physicians and patients prior to 1983 for the permanent, disabling and progressive risks of arachnoiditis associated with subarachnoid injection of Pantopaque for myelography.

Pantopaque's labeling from 1940 through 1980s repeatedly did not provide the treating physician with sufficient truthful and scientific information to adequately allow them an opportunity to make an informed risk versus benefit decision regarding the safety of using Pantopaque for imaging patients. Pantopaque's labeling consistently misrepresented the severity and frequency of "acute" and short-term risks as well as failed to adequately warn the physician of the increased "chronic" or long-term permanent risks of myelography associated with Pantopaque.

Lafayette Pharmacal's and Alcon Laboratories own animal testing and human experience data for Pantopaque, an oil-based contrast medium for myelography, demonstrated that Pantopaque was toxic when injected into the subarachnoid space. Reported symptoms and conditions associated with Pantopaque injection included intractable back and leg pain; bowel and bladder dysfunction; sexual dysfunction; paralysis; focal and grand mal seizures; blindness; shock; chronic adhesive arachnoiditis; chronic obliterative arachnoiditis; coma; and death. There is no known cure nor treatment for the many devastating chronic diseases and symptoms reported in patients following injection of Pantopaque.

"ARACHNOIDITIS"

According to the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Health (NIH), Bethesda, MD website, initially released **1996**, updated **May 2000:**

> **Arachnoiditis**: an inflammatory response of the arachnoid, one of the three coverings, or meninges, that envelop the brain and spinal cord. It may result from infection, including syphilis and tubercular meningitis, or trauma (including that resulting from surgery, lumbar puncture, and spinal anesthesias). A diagnostic procedure, called a myelogram, which is performed in patients prior to spinal surgery may cause numbness, tingling, and a characteristic stinging and burning pain. (* i.e. acute arachnoiditis.)
>
> **Treatment:** The goal of treatment should be to return the patient to a functional role in society. Conservative therapy such as pain management is generally recommended. In those patients whose arachnoiditis is progressive, surgery to remove adhesions is only minimally effective because scar tissue continues to develop. Also, surgery exposes the already irritated spinal cord to additional trauma.
>
> **Prognosis**: There is no cure for arachnoiditis. For the majority of patients, arachnoiditis is a disabling disease causing intractable pain and neurological deficits. As the disease progresses, some symptoms may increase and become permanent. Few people with this disorder are able to continue working. In some cases, progressive paraplegia may occur.
>
> **Research**: Within the NINDS research programs, arachnoiditis is addressed primarily through studies associated with pain research. NINDS vigorously pursues a research program seeking new treatments from pain and nerve damage with the ultimate goal of reversing debilitating conditions such as arachnoiditis.

The Management of Pain, J.J.Bonica, 2 edition, Lea & Febiger Publishers, Philadelphia, PA, **1990**, made the following points regarding the association of arachnoiditis and chronic pain, page 1276:

> Arachnoiditis, characterized by inflammation and fibrosis of the arachnoid membrane, is a well-recognized cause of chronic pain. Although the cauda equina is

the most common site, arachnoiditis can occur at any spinal level. It can be focal and involve only one root, thereby leading to a segmental pain syndrome with variable loss of sensory and motor function. Arachnoiditis can also affect multiple segments and lead to a more diffuse pain syndrome in the lower trunk and abdomen. The pain of arachnoiditis is constant but is worsened by physical activity. Often a dysethetic component is present, and paresthesiae are common. Patients often report both a deep aching and a superficial sharp jabbing pain. The type of pain is not ameliorated by narcotics.

Further discussion by the author of "arachnoiditis" that can involve the lower spine, or "cauda equina", pg 1521:

One of the most disastrous complications of disk disease, myelography, trauma, subarachnoid hemorrhage, infection, or spinal surgery is the development of arachnoiditis involving the cauda equina. It is not understood why only a small percentage of patients who have one of these inciting causes develop inflammatory changes in the nerve roots and the surrounding arachnoid. Furthermore, not everyone with the histological findings of arachnoiditis has a pain syndrome.

Etiology
Although any of the causes listed above can precede the development of arachnoiditis, none of them do so with any regularity. In addition to these factors, the following causative agents are thought to be involved: syphilis; bacterial, fungal, or disk space infection; intrathecal drug therapy; herniated nucleus pulposus; spinal stenosis; radiation therapy; intradural tumor; and spinal anesthesia. It is not known whether patients who develop inflammation in the arachnoid that progresses to fibrosis have an alteration in their immunologic responses. The initial inflammatory process can proceed to severe scarring, both within the arachnoid and within the nerve roots themselves. The process can be restricted to one nerve root or can involve various parts of the cauda equina.

Symptoms and Signs
The major problem with arachnoiditis is severe, unremitting pain in the lower back and legs. Varying degrees of motor and sensory loss can be present, and in some patients the scarring process in the arachnoid is associated with progressive, profound neurologic loss, although this is relatively uncommon. The pain is aggravated by movements or positions that stretch the lumbar nerve roots. Most patients say that exercise aggravates their pain and rest relieves it.

Diagnosis
The development of chronic low back and leg pain in a patient who has been exposed to any of the causative factors should lead to the suspicion of arachnoiditis. Patchy neurologic deficits that involve multiple nerve roots are common. Diagnostic studies should reveal the absence of other structural lesions and the presence of nerve root matting or clumping and filling defects in the arachnoid. This is often a diagnosis of

exclusion and is sometimes made without any real evidence.

Treatment
No controlled studies have demonstrated effective treatments for arachnoiditis. Some patients have responded to epidural and intrathecal steroids, usually administered with a local anesthetic. Because steroids do not affect collagen that has been laid down to form a scar, it is hard to explain their purported efficacy in arachnoiditis. Surgical lysing of the scarred nerve roots has also been undertaken, with variable results at best. Some patients lose neurological function after this operation. Because arachnoiditis is probably a form of deafferentiation pain, ablative surgical procedures are not indicated in most patients. Spinal cord stimulation has led to some symptomatic improvement in many but not all patients.

Page 1472, the same author in 1990 wrote regarding the "apparent decrease" that had occurred in arachnoiditis which he associated with the decrease use of "oil-based myelography":

Complications of Surgery or Diagnostic Studies.
All surgical procedures and invasive diagnostic studies can result in complications that perpetuate the patient's pain complaints and often add to the neurological abnormalities. Careful studies are required to identify preventable complications. One of the most disabling complications is arachnoiditis, which seems to be less common since the use of oil-based myeology has been replaced by the use of water-soluble media, CT scanning, and MRI. Surgical trauma, infection, inflammation, and bleeding can also lead to arachnoiditis. Not every patient with the pathological changes typical of arachnoiditis has low back pain, so much has yet to be learned about who hurts and who does not.

A physician performing myelography in the late 1940's through the 1980's and even today in 2002 would be generally aware that any diagnostic invasive spinal procedure, including myelography, carries some potential risk for a patient. All invasive spinal procedures potentially may result in complications that can perpetuate a patient's pain complaints and may produce future neurological abnormalities, including the spectrum of "arachnoiditis". Even in 1996 and 2000, the NIH indicated that myelography, a diagnostic procedure, performed routinely in patients prior to spinal surgery may cause numbness, tingling, and a characteristic stinging and burning pain, symptoms associated with an "acute" and " transient" arachnoiditis. Surgical trauma, infection, inflammation, and bleeding have also all been associated with the ability to produce symptoms attributable to arachnoiditis.

Research is still being done in the U.S. to help identify preventable complications of myelography and spinal imaging such as arachnoiditis. By 1990 and with the decreasing use of oil-based Pantopaque, there was also a corresponding decrease in arachnoiditis associated with spinal imaging. Since surgical intervention, bleeding, infection, trauma and spinal imaging were still occurring prior to 1990, each carrying its own anticipated rate of complications, the apparent decrease in new cases of arachnoiditis, helped support that injection of Pantopaque by itself had contributed its own unique "additive" role in the production of arachnoiditis.

Physicians and FDA in the 1940's through the 1980's were not informed by Lafayette Pharmacal and Alcon Laboratories in their Pantopaque labeling, agency communications or submissions, and communications of the true risks of intrathecal injection of the oil-based imaging agent, Pantopaque for humans. They were not told that the "risks" of Pantoapaque were seen in animal testing to be equivalent to the unacceptable "risks" of other oil-based imaging agents, iodinized poppy seed oil, the subject of the American Medical Association's 1932 warning to discourage its use in the subarachnoid space. The University of Rochester, Steinhausen's Ph.D research prior to FDA's approval in the 1940s and again in animal toxicity studies concluded by Hazelton Laboratories in 1969 with receipt of reports of serious patient injuries should have demonstrated or suggested to Lafayette Pharmacal that Pantopaque was associated with a "significantly increased" risk of producing permanent, progressive adhesive and/or obliterative arachnoiditis that would condemn certain patients to a lifetime of severe and unremitting pain.

When FDA was informed that Pantopaque was being withdrawn from the US market, the Agency was told that it was a management decision to discontinue the production and sale of an oil-based imaging product. FDA was not told that Pantopaque was being withdrawn due to litiginous association with serious, permanent and devastating disease, nor was FDA informed by the manufacturer that the firm had knowingly marketed a product from 1944 through the 1990s in the US aware that there was not sufficient safety data to support marketing. March 1990 discussions of FDA staff with news media regarding the "alleged" risks of injection of Pantopaque and apparent lack of safety, FDA's medical reviewer continued to advocate a clinical role for Pantopaque in imaging of US patients.

It is my opinion, within a reasonable degree of medical certainty, and based on my training and experience, that such negligent actions by Lafayette Pharmacal and Alcon Laboratories prior to 1983 directly contributed to the chronic Pantopaque-related spinal injuries reported within the U.S. population.

I reserve the right to amend my opinions.

Suzanne Parisian, M.D.