In 1966 Lafayette wished to withdraw IND 1-161 and submit a marketing application for Pantopaque II (15%) as a supplement to NDA 5-319.

However, the FDA did not accept this ?back door' proposal.

In April 1966, Herman, representing the FDA, wrote in his summary of NDA 16-377, that the request of the DTE review of 1964 (re: acute toxicity data and test with repeat does) had not been answered, no such test having been performed and no explanation proffered.

He noted that there were no case reports from any of the five groups of investigators in either the NDA or IND. Only the fifth group, Heinz, Brinker and Taveras of the Neurological Institute, New York, had presented a brief summary. Between 1963 and 1964, they looked at 117 patients who had received 15%, 22.5% or 30% Pantopaque.

They concluded that the less concentrated dye offered "definite advantages" but were unable to substantiate this claim with objective data or case reports. They published their results in a Swedish journal. ([1])

Herman concluded that the application was incomplete and that Lafayette had failed to report, in full, investigations, case reports or substantial evidence to adequately support their application.

A handwritten note by Ruskin of the FDA at that time queried the need to complete the pharmacological work prior to trials in humans.

Of course, Pantopaque in its original form had long been in use in humans by this time!

Herman replied to this note detailing the IND and sent a copy to the Investigational Drug Branch (IDB) and the DTE.

Whether any subsequent action was taken is unclear, but in June 1966 Casola of the FDA Manufacture Control Branch (MCB) stated that the application for Pantopaque II was incomplete.

This was again the case in October 1966, when his colleague Wilson wrote:

"lophenylate (sic) has been on the market for twenty years but deaths have been attributed to its use."

He concluded that the test needed repeating, that the application was incomplete and also queried the need to establish whether there might be a hypersensitivity reaction in some individuals.

In 1966, the US Drug Efficacy Study Implementation (DESI) was set up under the auspices of the National Academy of Sciences and the National Research Council (NAS-NRC).

This aimed to retrospectively study all drugs approved between 1938 and 1962 for efficacy.

Howland and Curry ([2]) presented their findings of their further dog study looking at blood and Pantopaque, and the effects of the steroid methylprednisolone which was being tested to see if it might help to prevent the inflammation.

They found that the steroid made no difference; Pantopaque, steroid and blood together brought about severe arachnoiditis in a third of the subjects.

Blood and dye (3ml of each as in the 1963 study) caused paralysis of the extremities in 50% and all showed severe inflammatory induration around cystic spaces, most in the lower cervical region (the site of the injection).

They suggested that blood acted by coating drops of the oily dye with fibrin, thus emulsifying it and provoking an inflammatory response.

In December 1966, Greig and Wignall ([3]) published a case report of arachnoiditis associated with Pantopaque myelography.

---

[1] Heinz ER, Brinker RA, Taveras JM *Acta Radiol Diagn (Stockh).* 1966; 5:1024-31 Advantages of a less dense Pantopaque contrast material for myelography.

[2] Howland and Curry *Radiology* 1966 Experimental Studies of Pantopaque arachnoiditis. 1. Animal Studies.

[3] Greig JH, Wignall N *J Can Assoc Radiol*. 1966 Dec; 17(4): 198-9 A case of arachnoiditis associated with "pantopaque" myelography.