In January 1944, Van Winkle further expressed his strong concerns in a letter to Bucke at Lafayette.

In particular, he noted that the proposed circular to accompany the product was unsatisfactory in various ways, especially,

"The entire circular creates the impression that reactions are infrequent and are of a minor character."

As Van Winkle mentioned earlier in the letter, in fact

"**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 with the use of this material."**

Van Winkle also remarked that the company appeared not to exert any chemical control over the drug after receiving the raw materials, and advised a further check on the finished packaged product.

He stated clearly:

"**on the basis of the reports contained within the application and without additional data, we hesitate to permit this application to become effective on the basis of its safety for use."**

Van Winkle was particularly interested in additional data comparing the nature and severity of reactions to iophendylate with those of Lipiodol.

The letter also stressed the need to make it clear to users of the product that

"reactions appear almost uniformly if the product is not removed following examination"

so that removal should be strongly recommended.

Shortly after this, Van Winkle received a letter from a Major Spurling, who strove to convince him of the safety of the new product.

The requested data from Strain was not produced and the initial NDA application by Lafayette was thus considered by the FDA to have been "withdrawn".

Within what now seems a disproportionately short period, on the 22nd. February, 1944, the NDA for Pantopaque was approved 'effective', with the condition that if the composition, dosage, or method or duration of administration or application, or other condition of use, were to change, an appropriate amendment to the application should be submitted for consideration.

This was signed by R.P. Herwick, M.D. Chief Drug Division.

FDA approval was granted in April, 1944, with the patent being issued in the May. This took place without any apparent resolution of Van Winkle's objections.

Strain meanwhile had demonstrated encysted retained Pantopaque in dogs.

However...

In October 1944, Spurling claimed that Pantopaque was absorbed in the body ([1])

He also dismissed the animal studies as "meaningless" and therefore eliminated the data from his report.

This would no doubt have meant that he discounted the results of Boldrey and Aird ([2]) who found chronic adhesive arachnoiditis at up to three months in animals after use of poppyseed or peanut oil, which indicated potential problems for a similar oily contrast medium such as iophendylate.

1944 labelling of Pantopaque was misleading on several counts.

For example, it claimed that side effects were only slightly greater than with ordinary lumbar puncture, were "transient", even if the dye was not removed, and that 80-90% removal could be achieved without much difficulty.

Already, at this stage, the company were blatantly misrepresenting their product.

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[1] Wyatt GM, Spurling RG, *Surgery* 1944; 26: 561 Pantopaque: Notes on Absorption Following Myelography

[2] Boldrey E, Aird RB *J Nerv & Ment. Dis.*1944; 99: 521 The Effects of iodised Poppyseed Oil and Iodine Chlorine in Peanut Oil on the Subarachnoid space of animals.