In 1967, in the UK, the Medicines Control Agency was established.

At this point, any drug that had been in circulation prior to 1967 was given a product licence of right without reports, which were required to be submitted at a later date (within a five year rule).

After this, individual products could be given exemptions.

In September 1967, Hazleton completed their intrathecal rabbit study, which aimed to show LD50 (dose at which 50% of the animals die).

In a letter to Fassett of the Laboratory of Industrial Medicine, Embree of Dpi, a subsidiary of Kodak, noted that the study did not look at Steinhausen's technique of head bending, which revealed meningismus; he also said that the proposed study was "entirely too short."

In November 1967, results from the acute intrathecal toxicity study of Pantopaque II were sent to Lafayette. Motor incoordination was observed (not dose related) as well as connective tissue lesions.

Nevertheless, the proposed 1967 Pantopaque II package insert read:

"Pantopaque II in rats, given intraperitoneally caused, ?no deaths and no toxic effects' and intrathecal injections in rabbits gave rise to "no... unusual or delayed damage to the spinal cord."

Meanwhile, Heinz, Brinker and Taveras' series of 74 patients apparently showed no

"detectable objective or subjective abnormality"

(inclusion of the word ?detectable' perhaps being a way of covering themselves.)

The source of funding of this study is likely to have been the manufacturers themselves.

In the same year, Embree of Dpi wrote to Jessup at the Hazleton Laboratories about the six-week time to sacrifice of animals studied.

He wondered if they should wait longer, and about the doses being used.

These queries seem entirely reasonable, but in the ensuing communications and studies, no account appears to have been taken of his concerns.

Fried and Skrzypczak published a paper written in German (thus perhaps inaccessible to American clinicians) on the later damage due to contrast media after Pantopaque myelography. ( [1] ).

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[1] Fried H, Skrzypczak J *Nervenzart* 1967 Jul; 38(7): 322-4 [Late damage due to contrast media after pantopaque-myelography]