Infected Blood Inquiry

Presentation by Counsel to the Inquiry

Pharmaceutical Companies: Response to Risk

Appendix: The Prince Controversy

1. In December 1984, Armour commissioned Dr Alfred Prince of the New York Blood Center to undertake studies on the efficacy of its heat treatment processes. The purpose was to determine whether a measured quantity of HTLV-III would be inactivated by the heat treatment regime that the company had adopted for its factor concentrates. **[ARMO0000343]**.

2. The approach proposed was to add a known amount of virus to the concentrate before it was freeze-dried (lyophilised) and heated. Following that process, the product would be tested to see how much residual virus it contained. Virus reduction was measured by determining how many logs of inactivation had been achieved (i.e. a sample in which the amount of virus is reduced in size by a factor of 10^4/ml has been subject to a 4 log reduction or *"kill"*). The industry standard at the time was a 5 log (10^5/ml) reduction.

3. It was expected that virus could be inactivated both by the freeze-drying process, and by the subsequent heating of the product. Armour's heating technique involved dry heat at 60°C for 30 hours. By way of comparison, Hyland's products were subject to dry heat at 60°C for 72-74 hours, and Miles/Cutter's to dry heat at 68°C for 72 hours.

4. Dr Prince provided the results of his first study in January 1985. He wrote that *"disappointingly … we were unable to show the > 5 log kill as had been hoped. The most that can be concluded from the study is that the combined effect of lyophilization and heating inactivated ≥ 2.5 – 3.0 logs."* **[ARMO0000356]**

5. Dr Prince's results were at odds with those that had been previously obtained from experiments conducted by the Centers for Disease Control ("CDC"). On 29 November 1984, Dr Bruce Evatt from the CDC had written to Armour giving the results of those studies, which indicated that heat treatment at 60°C for 24 hours had

left no detectable virus in a sample of Factor VIII concentrate. His letter concluded **[MDUN0000020_250, ep.13, §58]**:

> "Because LAV [HTLV-III/HIV] appeared to be extremely heat labile, we believe that the procedures presently used by the manufacturers for heat treatment of hepatitis virus would adequately inactivate the LAV virus."

6. The CDC results were subsequently published in the *Journal of Clinical Investigation* in August 1985. The lead authors were Dr Evatt and his colleague, Dr Steve McDougal **[MDUN0000020_250, ep.13, §60]**. In October 1985, they joined with Dr John Petricciani of the FDA in writing a letter to *"The Lancet"* advocating the heat treatment of products on the basis that heating at 60°C for 20 hours would result in a 20 log reduction **[MDUN0000020_250, ep.15, §65]**.

7. Armour was, therefore, left with conflicting studies concerning the safety of their heat treatment process.

8. In an internal company memorandum on 11 February 1985, Dr Michael Rodell identified limitations in Dr Prince's study, in particular in respect of the low quantity of active virus that was included in the sample that was used. Dr Rodell considered that, *"the experiment should be considered preliminary in nature."* He noted that Dr Prince's team had been provided with samples with higher levels of virus, which would be used in further experiments within the coming weeks **[ARMO0000361]**. The company would also go on to commission further studies from other respected sources **[MDUN0000020_250, ep.21, §97-99]**.

9. Dr Prince conducted his further studies and reported them to Armour during the course of 1985. His findings were that *"pasteurization at 60°C in the dry state had only a modest process efficacy for inactivation of HTLV-III/LAV"* **[PRSE0004828, ep.4]**. This, he noted, was in marked contrast to the results obtained by Dr McDougal and the CDC, something that was *"difficult to explain"*. The implication of Dr Prince's results, though, was that Armour's established heat treatment process may not be sufficiently robust to inactivate HTLV-III.

10. Dr Prince wanted to publish his results, and sent a draft article to Armour **[PRSE0004828]**. The company invoked a clause in their contract that required him to obtain Armour's approval for any publication. That approval was not forthcoming. Dr William Terry discussed the situation with Dr Prince, and gave his recollection of the meeting in a memorandum dated 8 November 1985 **[CGRA0000512]**.

> "I told Dr Prince that while our foremost concern was the safety of patients receiving these products, these data taken in isolation could only be confusing to the scientific community, the treatment community and the public and that we therefore were not prepared to give him permission to publish. I pointed out the discrepancies between both his test system, and his test system results when compared with the data reported by McDougal and others. I indicated that we certainly wished to continue working with him and hoped that we could do a more comprehensive study, utilizing his sensitive test system, but applying it to the heating conditions and the products of the major suppliers.
>
> While Dr Prince was obviously disappointed and somewhat contentious, he accepted the fact he would not be able to publish these data and the conversation ended on a reasonably cordial note."

11. In later litigation Dr Prince said that he had been annoyed with Armour **[MDUN0000020_250, ep.18, §86]**. He set out to repeat the experiments outside of this contractual work with the company so that he could publish his results. On 31 May 1986, in a letter to the *"The Lancet"*, he did so. He found that viral inactivation from heating at 60°C was, on its own, *"surprisingly modest"*. Viral inactivation of between 0 and 1 log was measured when the sample was heated for 10 hours, with between 2 and 4 logs observed after 72 hours of heating. Lyophilisation on its own resulted in an additional 0.5 to 1 log of inactivation. He concluded **[PRSE0002534]**:

> "The finding of only modest sterilisation process efficacy for HIV adds to concern about the efficacy of this procedures. It should, however, be stressed that this finding does not mean that dry-heat treated products are unsafe with respect to transmission of AIDS. Indeed three studies have reported absence of anti-HIV seroconversions in recipients of dry-heat treated FVIII preparations. Purification and processing steps beyond lyophilisation can remove or inactivate virus, and lyophilisation alone under commercial conditions probably inactivates more virus than is observed with shell freezing. Nevertheless, these findings indicate the need for caution in relying on the efficacy of dry-heat sterilisation. Long term surveillance of recipients of such products for seroconversion to anti-HIV is still required."

12. The approach taken by Armour to Dr Prince's work has been a source of intense controversy for decades, not least because heat treated Factorate came to be associated with a number of seroconversions and was withdrawn from sale in the UK (but not other international markets) in September 1986 **[ARMO0000217]**. Dr Peter Jones, giving evidence to the Lindsay Inquiry about a meeting of Armour scientists and executives held in October 1985,[1] wrote that the company **[PJON0000028_001, ep.9]**:

[1] Minutes of the Recombinant Steering Committee, October 15, 1985 **[CGRA0000513]**.

> "appear[ed] to consider it ethical to continue to market unsafe product whilst attempting to manipulate the results of their laboratory tests in order to throw doubt on the safety of their competitors' products in the eyes of the FDA. They are doing this in order to protect their share of the market."

13. In his report, Mr Justice Krever found that as well as prohibiting publication, Armour chose not to inform the Canadian Bureau of Biologics, the relevant regulatory body, about Dr Prince's findings. In his view **[KREV0000001, ep.529]**:

> "Armour's obligation was to convey safety-related information about its products to the bureau promptly. It could have addressed risk, if any, of confusion by including in a timely report to the bureau all the contradictory and inconsistent data it believed qualified Dr Prince's findings."

14. A criminal case was later brought in Canada against Armour and Dr Rodell (among others), in which the prosecution alleged that there had been a duty to disclose Dr Prince's studies **[MDUN0000020_250]**. The case was heard by Madam Justice Benotto. She acquitted the defendants, and came to a different conclusion to Mr Justice Krever. In her view, Armour and Dr Rodell had been justified in their position, particularly in light of the other studies that the company had considered and commissioned on the efficacy of its heat treatment process **[MDUN0000020_250, ep.19, §90]**:

> "This was a time of great uncertainty. In the face of this, and in light of the clearly articulated studies of the CDC, supported by the FDA, it would have been unreasonable, if not irresponsible, for Armour to have thrust such confusing, incomplete and inconclusive information into the community."

15. She acquitted the company and Dr Rodell on all charges, commenting that *"the conduct examined for over one and a half years confirms reasonable, responsible and professional actions and responses during a difficult time"* **[MDUN0000020_250, ep.64, §305]**. Dr Rodell, she found, *"was responsible and professional throughout, consistent with his well-deserved reputation for integrity"* **[MDUN0000020_063, ep.63, §304]**.

16. This presentation does not attempt to scale the mountain of evidence and opinion that have formed in the wake of a result of a controversy lasting more than thirty years. Several of the protagonists had given extensive testimony about what happened. Previous inquiries have considered and commented upon the matter.[2] The technical details involved – from the sensitivity of assays, to alleged arithmetic

[2] See, for example, **KREV0000001, ep.497-529**.

errors in calculations, to questionable assumptions that underpinned conclusions – are complex and require careful scrutiny. For present purposes, it is enough to sketch from afar the contours of the debate.

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