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From: J G Booth MB6B
Date: 15 November 1989
Copy: Mrs Rabindran MB6B

"PROFILATE" - ALPHA THERAPEUTICS CORPORATION

1. The meeting arrangements for Thursday 16 November at 3.30 pm on the 19th Floor at Market Towers are confirmed.

2. The attached extract from the note of the Inspection Action Group meeting on 13 November is circulated as background information to aid discussion.

GRO-C

J G Booth
Room 1814 MT
Ext GRO-C

Dr Jones
Mr Wilson
Mr Franks
Mr Ayling
Dr Kavanagh
Miss Hepburn
Dr Rotblat
Dr Fowler
Mr Nilsson
Mr Freedman
Mr Luxton PD
Mr Dobson HS 1
Dr Pickles MED-H
Dr Rejman MED-H
Ms Jenkins ED
NIBSC

17 NOV 1989
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"EXTRACT"

IAG(10)89

INSPECTION ACTION GROUP
NOTE OF A MEETING HELD ON 13 NOVEMBER 1989

Present:	Mr Franks	(Chairman)
	Mr Booth	
	Miss Hepburn	
	Dr Fowler	
	Mr Turner	(Vice Mr Ayling)
	Mr Holloway	
	Dr Kavanagh	
	Mr Freedman	
	Mr Burton	
	Mr Sloggem	(Attended for Item 5 Only)
	Mrs Reenay - (HS1A)	" " " " "
	Mrs Richter	
	Mrs Rabindran	(Secretary)

Apologies for absence were received from Messrs Ayling and Bromley (MAFF).

5. ALPHA THERAPEUTICS CORPORATION - USA

5.1 Alpha Therapeutics is a subsidiary of the Green Cross Corporation of Japan. A comprehensive range of blood products is made at the Los Angeles site. The site was inspected on 6-10 October 1989. The inspection which covered the manufacture of Blood Products, the sterilization and filling into dose form containers, and the pasteurisation of those finished products, revealed that the Company had failed to correct a major deficiency found at the previous inspection in February 1988, in spite of indicating that they would do so, in order to ensure the production of viral-free Factor VIII "Profilate".

5.2 Dr Kavanagh (Principal Medicines Inspector) explained that the company in common with other commercial blood products manufacturers, employed a viral-inactivation procedure at a bulk intermediate stage, rather than a terminal pasteurisation step. A consequence of using such a method was that the product then had to be protected from possible re-contamination during the remaining stages of processing. This was generally achieved by handling virus-inactivated material in specially-constructed, isolated areas, equipped with their own independent air-supply, dedicated equipment and dedicated staff clothing. Alpha-Therapeutic had built such an area where they prepared their Factor VIII product for the US market.

The Profilate material for the UK, however, was made differently. The virus-inactivation step involved heating a slurry of freeze-dried Factor VIII in heptane; the equipment for this and the area in which it was sited made it

extremely likely that heat-treated Factor VIII would be re-contaminated with untreated Factor VIII and/or albumin, with the concomitant risk of possible viral contamination.

Dr Kavanagh described the process and conditions as detailed in the Inspectorate report, and explained that, following the February 1988 inspection, the company's response was that they would investigate ways to isolate the area and fit an independent air-supply system; also that they would be submitting imminently a UK PL application for the USA-type product which was made in the viral controlled area.

The inspection in October 1989 showed that nothing had been done; in fact the situation was worse in that the amount of untreated Factor VIII powder present in the heat-treatment room was much greater. In addition, the PL application for the new product had not been submitted. (Received since the inspection report).

The company's response to the 1989 inspection remain unsatisfactory; the changes to procedures, while an improvement, were mainly cosmetic and did not address the main problems of a shared air-supply, absence of air pressure barrier and the open handling of treated and untreated Factor VIII powder in the same room. The company acknowledged that the UK product was inferior to that marketed in the US. The Inspectorate recommended withdrawal of the PL for Profilate as the method used to produce it did not ensure a virus-free product.

5.3 The Group then discussed whether the removal of the licence would cause a supply problem since the Company had indicated that they supplied well in excess of 80% of the UK Commercial Factor VIII requirements.

Mr Burton (PD/STD) explained that Factor VIII was a licensed hospital only product. He had investigated the Company's claim and established that the Blood Products Laboratory (BPL) supplied about 70% of the UK requirements, and 30% of the commercial market was supplied by Alpha and Miles-Cutter. The situation was, that Alpha only supplied 80% of 30% of the commercial market. Therefore Mr Burton considered that there would be no supply problem. However, he referred to earlier problems at BPL and asked whether they were in a position to meet the shortfall. Dr Kavanagh stated that he understood the deficiencies at BPL had largely been resolved and production procedure had improved, and it was likely that no difficulties would be encountered in this respect. Miss Reenay indicated that this was also HS1 understanding of the supply situation. Other suppliers mentioned were Baxter, Immuno and Speywood.

5.4 Mr Sloggem (Principal Pharmaceutical Officer) confirmed that there would be alternative supplies in the near future. Two PL applications for Blood Products using the solvent detergent system, namely Monoclate P were to be considered by the Committee for Safety of Medicines (CSM) in November 1989, and were expected to be approved. A Koate HS product licence application was to be submitted to the Biological Sub-Committee and CSM in January 1990. A CTX was in being for the new detergent system. The variation application from Alpha for Profilate which had been received in early November 1989, was to be submitted to the CSM, possibly in January 1990. The Medicines Inspectorate commented that if the variation was approved the GMP for the product was likely to be acceptable.

5.5 In view of the critical nature of the problem the Group discussed the possibility of suspending the PL immediately. Mr Freedman's (Solicitor) view was that a serious threat to life would justify immediate suspension of the licence under paragraphs 10 and 11 of Schedule 2 of the Act, with concurrent S28 action to follow. This was required under paragraph 13 of Schedule 2 to provide the company with appeal rights and to suspend the licence for a further adequate period until the variation was approved. Dr Fowler supported the proposal, pointing out that the product was an extreme patient hazard as it could be potentially AIDS contaminated material. The Medicines Inspectorate added the the Company had admitted the UK product was inferior to the US product. Miss Hepburn queried why formal action had not been taken after the 1988 inspection. It appeared that the Company's activities had been condoned for almost a year. The Inspectorate pointed out that the company's assurances of improvement had been accepted and they had given the Company time to put their house in order, but the recent inspection revealed that the problems had not been sufficiently addressed. The situation had in fact deteriorated and was now unacceptable. The Group agreed on immediate suspension of the product licence.

5.6 The Chairman explained that in taking this action it may be necessary to effect a recall of all available material. He reminded the Group that the licensing authority could require a product to be withheld from sale only for a period of 6 weeks. In the absence of other withdrawal powers this would call for the co-operation of the manufacturer. He invited the Group to consider. There was general agreement that, in the light of the information available such action was appropriate. Dr Kavanagh did not foresee any problems in this sphere.

5.7 Miss Reenay expressed concern about the publicity which a Drug Alert would attract. She asked for HS1 to be involved in drafting the Alert message. They were likely to consult legal advisers. She confirmed the understanding that, while the product was 'hospital only', haemophiliac patients would have received supplies from consultants and stored these in home refrigerators. It would be possible to identify patients by registration.

5.8 The Chairman reminded the Group that,in addition to the normal procedure whereby the proposals would require clearance with the top of MCA, this particular case was likely to be referred to Ministers before action took place.

5.9 The Group agreed:-

i. to recall all available Factor VIII material manufactured by Alpha. Medicines Inspectorate to seek manufacturer's agreement.

ii. the immediate suspension of the PL under paragraphs 10 and 11 of Schedule 2 to the Act.

iii. a proposed suspension of the licence for a further period of 6 months until the PL variation application had been approved.

iv. to liaise with HS1A at all stages.

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