RESTRICTED

1. Dr Metters
if you agree:
2. Mr Davey PS/MS(H)

From: Mr Wilson MCA
Date: 24 November 1989
cc: Mr McKeon PS/SofS
Mrs Kirk PS/PS(H)
Mr Rayner FPS/M
Miss Pease HS
Dr K Jones MCA
Dr H Pickles ISD
Dr Rotblat MB3A
Dr Fowler MB3A
Mr Hartley MB5B
Mr Ayling MB5B ->
Dr Purves MB5A
Miss Hepburn MB5A
Mr Nilsson SolC5
Mr Franks MB6
Mr Booth MB6B
Mr Dobson HS1
Mr Luxton PD

FACTOR VIII - PROFILATE

SUMMARY

This submission informs MS(H) of an adverse inspection report relating to the manufacturing standards for a commercial factor VIII blood product PROFILATE, marketed in the UK by a US based firm, Alpha Therapeutic Corporation. The potential risks to health are not considered by officials to warrant any immediate regulatory action eg to suspend marketing or withdraw stocks. But it is proposed to take steps to persuade the company to discontinue to supply PROFILATE made by the process currently used for the UK market.

BACKGROUND

The Product

1. PROFILATE is marketed by the Alpha Therapeutic Corporation based in Los Angeles and owned by the Green Cross Company of Japan. It has been licensed in the UK since 1985. The Blood Products Laboratory (BPL) now provides about 70% of the market in England and Wales and PROFILATE possibly about 20%. In recent years before BPL facilities were developed PROFILATE supplied a larger proportion of the UK market. It has also been widely marketed internationally. It has a good 'track record' for quality and safety.

Inspections

2. In February 1988 the Medicines Inspectorate of the Department carried out an inspection of the plant facilities used for PROFILATE. They listed 4 major deficiencies which the company assured them would be dealt with. These included deficiencies relating to the risk of recontamination of heat treated Factor VIII powder by untreated powder because of inadequate arrangements for the separation of the different stages in the treatment process. At the time of this inspection the heptane heat treatment process used by Alpha was considered to be the best of available methods then in commercial use. The deficiencies identified related to the way the company operated the process not the process itself. It seems most probable that these deficiencies had existed at least since the product was licensed in the UK in 1985.

3. Subsequent monitoring of the situation indicated that whilst the other deficiencies had been dealt with the situation giving rise to the risk of recontamination had not. A second visit by the Inspectors in October 1989 confirmed that the deficiency still remained and that conditions had deteriorated. On receipt of a further adverse report following that inspection the company say they have instituted a number of changes which should reduce but will not eliminate the risk.

Alternative Process

4. PROFILATE marketed in the US is now produced by a new method different to the heptane treatment method still used for the product marketed in the UK. The new method is claimed to produce a superior, ie safer, product. The company have recently applied to have their UK product licence varied so as to market the US version in the UK. The US version is made in separate new facilities. It seems likely that the company have been reluctant to spend substantial sums on upgrading the heptane process when they planned to switch production to the new facilities.

RISK ASSESSMENT

5. PROFILATE produced by the heptane treatment process has been widely used in the UK and elsewhere for a number of years. The deficiencies in that process revealed by the inspection report are of similar long standing.

6. If any of the heptane treatment PROFILATE has been contaminated as a result of processing deficiencies, the theoretical risks include:-

a. Hepatitis B

b. Non A, non B hepatitis

c. HIV

7. The data about infections in haemophiliac patients is relatively well documented because of the comparatively small numbers and the specialised hospital centres dealing with them, which mean that treatment can be closely monitored. Relative risks of different products used by haemophiliac patients can accordingly be assessed with more confidence than in other areas.

Hepatitis B

8. There is no clinical evidence in the UK of hepatitis B transmission from PROFILATE. Most patients are immune due to previous infection or vaccinations so the 'at risk' pool of patients is small. All donor blood is tested for the hepatitis B virus as well as for HIV antibodies.

Non-A, non-B hepatitis

9. PROFILATE produced by the heptane treatment method is a 'first generation' factor VIII product and all these products are associated with some risk of transmission of non-A, non-B. But there is no evidence to suggest any higher risks from PROFILATE than from other first generation products. Indeed a study (at the Royal Free) on patients previously untreated with factor VIII suggests that PROFILATE has a very low transmission rate for non-A, non-B hepatitis.

HIV

10. The theoretical risk cannot be ruled out but there is no evidence of any HIV transmission in the UK by this product, nor of any such case outside the UK.

Reference Centre Directors

11. We have been in touch in confidence with Dr Rizza, Director of the Oxford Haemophilia Reference Centre (who is also chairman of the directors of the UK Haemophiliac Reference Centre). He has confirmed that heptane treatment PROFILATE has performed relatively well and was regarded often as the preferred option for patients starting on factor VIII treatment. He was not aware of any clinical evidence that heptane treatment PROFILATE is or has been less safe than other Factor VIII products. He was most concerned to avoid any additional pressures on haemophiliacs and their doctors at this time and hoped that there could be a low profile resolution of any perceived problem.

REGULATORY ACTION

12. The company has failed over a period of some 20 months, to deal effectively with a major deficiency in their manufacturing process which could affect the safety of their product. In spite of the lack of evidence to suggest that heptane treatment PROFILATE has been associated with any abnormal levels of infection MCA have considered whether regulatory action should be taken. This would involve suspension of the product licence, if necessasry with immediate effect. If immediately suspended it would be logical also to arrange a recall of stocks from hospitals and patients (some will have stocks in fridges at home). Indeed such a step would be virtually inevitable.

13. Such action would remove very quickly any prospect of further exposure of haemophiliac patients to heptane treated PROFILATE. It is likely that BPL could, at least for some months, meet the shortfall in supply though it is also likely that there would be increased use of other commercial products, some not yet licensed and some may have a less good clinical safety record than PROFILATE.

14. However the clinical record of heptane treatment PROFILATE does not suggest that, on safety grounds, the evidence is there to warrant immediate suspension. Such action would also give rise to great anxieties amongst the haemophiliac community, a very high percentage of whom will have used PROFILATE at some stage. It would not be possible to assure them that the problems related only to recent production. Many would also currently be using PROFILATE. There would be much attendant publicity. Questions would be asked as to why, if suspension is necessary now, the action was not taken when our inspectors first became concerned in February 1988, insofar as the deficiencies then found have not fundamentally changed.

15. Non-immediate suspension would provide the company with time to exercise their right of appeal before the decision becomes public and took effect.[1] This appeal would probably be in private but knowledge of it could become public. The final decision whether or not to confirm the suspension would be for Ministers (as the Licensing Authority). If the product were suspended following an appeal the attendant publicity might be less than with immediate suspension but the difficulties could be of the same order with questions also as to why, if there were safety concerns, action had not been taken earlier.

ALTERNATIVES TO REGULATORY ACTION

16. The company is known to want to switch production for the UK market to its new process (para 4 above). It cannot market PROFILATE made by this process in the UK until its product licence has been varied. However it is possible that the company could be persuaded to begin withdrawal of the heptane treatment PROFILATE ahead of marketing of the new process product here, for commercial reasons. Whilst not making any deal with the company we could also expedite processing the application to vary their UK licence (though it may take some months even so). The company might be helped in reaching its decision if they believed that regulatory action might be taken against their licence if they do not act voluntarily.

---

[1]The company would have a right under the Medicines Act to make representations to a 'person appointed' by the Licensing Authority. These are formal hearings in private followed by a report of the proceedings to the Licensing Authority. The hearing would be in private unless the company wished otherwise. The report is private.

CONCLUSIONS

17. MCA and HSI, with their medical and legal colleagues and the Procurement Directorate have considered the issues.

18. As noted above they have concluded that, whilst the process deficiencies revealed by the Inspectorate are a cause of concern, the clinical record of heptane treatment PROFILATE does not suggest that these apparently long standing deficiencies are such as to warrant immediate regulatory action against the product.

19. They concluded that a better alternative would be to open discussions with the company with a view to securing early withdrawal of heptane treatment PROFILATE plus action to speed up consideration of the company's application to vary its PROFILATE licence so as to market the newer version of the product now sold in the US.

20. MS(H) is invited to note these conclusions and to say whether she endorses them.

GRO-C

C H WILSON
Medicines Control Agency
Room 1031 MT
Ext GRO-C