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Dr Rotblat MB3A
Dr Fowler MB3A
Mr Ayling MB5B
Miss Hepburn MB5A
Mr Nilsson SolC5
Mr Franks MB6
Mr Booth MB6B
Dr Pickles ISD
Mr Dobson HS1
Mr Luxton PD

From: Mr Wilson MCA
Date: 21 November 1989

cc: Dr Metters
Dr K Jones MCA

PROFILATE

I attach a draft submission to MS(H) following last Thursday's meeting. I'd be glad to have comments by close on **Wednesday 22 November.**

GRO-C

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

Enclosure

Mr Cameron No.
I only have a minor comment on para 15. Anything you want to add?

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D.K.

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1st draft

Mr Davey

From: Mr Wilson MCA
Date: 21 November 1989

cc:

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 stock supplied to the UK market.

BACKGROUND

The Product

1. PROFILATE is marketed by the Alpha Therapeutic Corporation based in Los Angeles. It has been licensed in the UK since [ ]. The Blood Products Laboratory (BPL) now provides about 70% of the UK market and PROFILATE about 20-25%. In recent years before BPL facilities were developed PROFILATE supplied about 70% 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.

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. On receipt of a further adverse report following that inspection the company say they have instituted a number of changes which should reduce the risk but the fundamental weakness of the system remains and the risks have not been eliminated.

Alternative Process

4. PROFILATE marketed in the US is produced by a new method not involving the heptane treatment method still used for the product marketed in the UK. 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. The theoretical risks from contaminated Factor VIII 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.

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. 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 had no adverse comments.

REGULATORY ACTION

12. MCA have considered whether, in spite of the lack of evidence to suggest that heptane treatment PROFILATE has been associated with any abnormal levels of infection, regulatory action should be taken. This could include suspension of the product licence, if necessary 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).

13. Such action would remove very quickly any prospect of further exposure of haemophiliac patients to heptane treatment 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 (on a named-patient basis) and some of which may have a less good clinical safety record than PROFILATE.

14. However immediate suspension would give rise to great anxieties amongst the haemophiliac community, a very high percentage of whom will have used PROFILATE at some stage. It will be impossible to assure them that the concerns which led to suspension relate only to recent production. Many would also currently be using PROFILATE. There would be much attendant publicity, fuelling present public concerns over financial help for haemophiliac patients with HIV infection. Questions will 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 any public announcement.[1]. This would be in private but knowledge of it could become public: the final decision whether or not to confirm the suspension would remain 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.

Public criticism could be worse if suspension delayed !

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[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. Both the hearing and the report are private.

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 if they do not act voluntarily.

CONCLUSIONS

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

18. They have concluded that, whilst the process deficiencies revealed by the Inspectorate are a cause of concern (as is the company's lack of effective remedial action), 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. In reaching this conclusion they had regard to the impact on haemophiliac patients, who had used the product extensively in recent years, which suspension would have and which would be likely to cause serious concern disproportionate to the likely real risks involved. They also had regard to the possibility that, if heptane treatment PROFILATE were suspended some haemophiliacs would be treated with some commercial products with a less good clinical safety record.

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. They would not rule out regulatory action if the company is not prepared to expedite withdrawal of the present product voluntarily.

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

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