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(See Annex C at Back)

FACTOR VIII - APPLICATION BY ARMOUR PHARMACEUTICAL CO. LIMITED.

1. This submission concerns the application for a product licence under the Medicines Act 1968 by Armour Pharmaceutical Company Limited in respect of Factorate, their brand of the antihaemophilic factor (Factor VIII). The application was considered by the Committee on Safety of Medicines (CSM) at their meeting in November 1975; they advised that a product licence should be granted subject to the acceptance by the company of certain conditions. No action has yet been taken on this advice.

SUMMARY OF APPLICATION.

2. Armour Pharmaceutical Co., Limited submitted a product licence application for Factorate on 2 April 1975. The application states that:-

(a) Manufacture and labelling takes place at the factory in Illinois USA, of the applicant's American parent, Armour Pharmaceuticals, Inc.

(b) Factorate is manufactured from fresh frozen human plasma which when tested is found to be negative for hepatitis B Antigen activity.

(c) Human plasma for this purpose is supplied by blood collection clinics licensed by the US Food and Drug Administration (FDA) and by non-licensed clinics (that is to say clinics outside the USA). Both licensed and unlicensed clinics are required to comply with the Code of Federal Regulations affecting the supply of human plasma.

(d) Each donation is checked for freedom from hepatitis associated antigen by radioimmuno assay and each batch of blood fraction is subject to batch release procedures in accordance with the rules laid down by the Bureau of Biologics of the FDA.

(e) Labelling will contain a warning to the effect that the product is prepared from pooled human plasma and that despite careful selection of donors it may contain causative agents of viral hepatitis. (Similar warnings appear on other company's products).

COMMITTEE ADVICE.

3. The CSM, on the recommendation of their Sub-Committee on Biological Products, advised that a product licence be granted subject to the following:-

(a) Further details being provided by the applicant as to the method of assay, the standard used and the calibration, and as to batch reproducibility.

(b) The following conditions being observed:-

(1) Information should be provided by the licence holder on

(i) The number of donations from which plasma is pooled for the manufacture of each batch of product.

(ii) The reasons for and rate of rejection of donors or donations, centre by centre.

(2) The potency of the products to be expressed in international units.

(3) The product is to be stored at a temperature of 6^{0} centigrade or below.

(4) Product labelling is to be in accordance with the British Pharmacopoeia for dried human Antihaemophilic Fraction. (See annex A).

(c) Each batch of the product would be subject to the batch release procedure. Under this the licensing authority has power to ask for the submission of samples of and protocols for each batch and to impose restrictions on the sale of the batch until the samples have been tested and the protocols examined by the National Institute of Biological Standards and Control(NIBSC) at Hampstead.

LICENSING ACTION.

4. The normal action on receipt of advice by the Committee in these circumstances would be to invite the company to amend their application - to incorporate the conditions proposed. If they agreed a licence would then be issued on this basis. If the applicant did not agree the conditions could not be enforced without first giving the company the opportunity of appearing before or making written representations to the Committee.

5. In view of the Minister's interest action on the lines has not yet been taken and we have considered whether any other conditions would be appropriate.

INSPECTION.

6. A representative of NIBSC has recently visited the fractionation plant but there has been no formal inspection by DHSS either of the plant or of the premises used for collection. In the light of experience of inspection of other companies producing blood products in the USA it is not considered that time and money would be well spent in inspecting the clinics where blood is collected. Inspectors could be shown only the best and even the worst might be run highly efficiently on the day of visit. While an experienced inspector might deduce the truth there can be no certainty of this. It seems best to assume that all blood products of this nature coming from the USA may be obtained from plasma taken under the worst circumstances and any protective measures should be achieved by other means.

7. The applicants are of high repute as manufacturers. Visits need only be made to the fractionation plant in order to verify the ability of the quality control staff to carry out the necessary tests and assays and, in cases of dubiety, to verify the records held at the centre and to ascertain that information supplied to the licensing authority in the UK is substantially correct.

8. The applicant has been required, in accordance with Section 19(3) of the Act to give an undertaking to permit the premises to be inspected by or on behalf of the licensing authority. If a licence is granted, inspection visits can therefore be undertaken at any time to Armour's premises.

9. This undertaking does not however extend to premises not belonging to Armour (in the USA or not) where the donations are taken. It might be prudent to secure a similar undertaking on the inspection of such premises.

10. Both the manufacturing premises and the collection centres (whereever situated) are subject to inspection by the FDA. There are however grounds for doubting whether the stringent provisions of US law are in fact fully enforced. In this connection Dr Theodore Cooper, US Assistant Secretary for Health, has written to the CMO about US procedures (ANNEX B) and it should be possible in the ensuing correspondence to obtain further information on this point.

SOURCE OF DONATIONS.

11. It may be worth considering whether limitations should be placed on the sources from which blood is obtained.

12. One possibility would be to authorise the marketing of the product only if it is derived from blood given by volunteers without payment. It is understood that over 50% of blood used in the USA is given voluntarily. It seems likely however that a restriction of this nature would affect the economics of the supply arrangements and would be unacceptable to the applicant. In any case it might be difficult to show that in fact blood from paid donors is necessarily less safe than from unpaid donors.

13. An alternative approach would be limit the sources geographically. The licence could relate to material obtained either at -

(1) licensed clinics in the USA.

(2) Centres in other named countries, specifically approved by the UK licensing authority.

14. On this basis, approval would be given in respect of other countries if sufficient was known of the local conditions including enforcement arrangements to give some confidence in the product. The point is that in the USA each clinic must be specifically licensed and therefore presumably some check is carried out. For collecting centres outside the USA all that is known is that they are open to inspection by the Bureau of Biologics, but in view of the distances involved it is unlikely that all centres are inspected regularly, if at all.

15. Such a condition could be combined with the condition envisaged in para 9 as to the undertaking to allow inspection of donation centres, the approval under para 13(2) being conditional on the giving of such an undertaking.

16. Here again, it is possible that the applicant would be unwilling to accept such a condition for commercial reasons but the limitation would appear to be practicable.

GENERAL CONDITIONS.

17. There are at present regulations under the Therapeutic Substances Act (TSA) about the manufacture of blood products. These were made many years ago, but were not of any practical effect until importation began - because they were not regarded as legally binding on the Crown, the only effective supplier. They cover basic requirements, including the medical supervision of collection and checking the health of donors.

In this respect they are more stringent than the U.S. regulations but in general they are much less detailed and do not incorporate references to modern test requirements.

18. These TSA regulations are in any case about to be superseded by new provisions under the Medicines Act and it seems desirable that the opportunity should be taken to give effect to more up to date and specific requirements on the general lines of the US regulations. In so far as the products are already subject to these regulations, this will make no practical difference but it will assist in dealing with products imported direct into the UK from countries other than the U.S.A.

OTHER SOURCES OF SUPPLY.

19. Three other companies have product licences in respect of imported Factor VIII and two other applications are under consideration. Brief particulars are given in ANNEX C.

20. In addition Factor VIII is now available from the UK National Blood Transfusion Service. Until recently the Medicines Act controls were not applied formally to NHS production. Arrangements for its application were promulgated in the Summer of 1975; these involved administrative measures in England and Wales and formal licensing in Scotland. In fact however at the present moment no formal action under the Medicines Act has been taken in respect of the preparation of Factor VIII. Although it is not suggested that anything is amiss in this connection, it must be borne in mind that some embarrassment might arise if an applicant were to ask whether the UK product had received the same scrutiny as his product.

21. If any of the additional requirements mentioned in this submission are to be added to the Armour licence it would clearly be right to impose the same conditions in respect of other similar products. New general requirements as contemplated in para 18 would achieve this result. Alternatively the companies could be asked to accept the conditions individually and if they did not action could be taken under Section 28 (3)(h) of the Medicines Act to vary the licences on the grounds that the standards are no longer satisfactory.

MATTERS FOR DECISION.

22. It seems necessary first to decide whether a visit of inspection should be carried out before determining the licence application. If, as suggested in para 6, it is agreed that no visit should be made at this stage, decisions are sought as to whether the company should be asked, in addition to the conditions proposed by the CSM, to agree that -

(a) Plasma should be obtained only from donor centres in the USA, or in other countries specified in respect of which the licensing authority is satisfied as to the arrangements (para 13).

(b) DHSS Inspectors may visit collecting centres (paras 9 and 15).

23. The Minister of State is asked to agree that subject to the company accepting the conditions proposed by the CSM and conditions (a) & (b) above, if he considers them appropriate, a product licence should be granted accordingly.

24. Agreement is also sought to the proposition that, as outlined in para 21, such conditions should be applied to other licence holders.