TELEFAX MESSAGE

TO

Name :	Mrs. Joyce Boult
Company :	Bayer
Location :	U.K.
Telefax No. :	GRO-C

Date :	July 5, 1988
Number of pages this transmission:	6

FROM

Name: Elias L. Greene
EG-8.311

Cutter | MILES

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Re: Trip Report

Enclosed is a draft of my trip report. Please send me any corrections, comments, etc. as soon as possible so I may issue the report.

Carol Moore is out until 7 July. I cannot obtain Lyn Christopher's telephone number until then.

Regards,

GRO-C

ELG/jwm

encl.

July 1, 1988

Visit to Bayer U.K.

Elias L. Greene EG-8.302 cc: Joyce Boult - U.K.
L. Ambrus

Carol Moore

I met with Mrs. Joyce Boult, Registration Manager, Pharmaceutical Business Group, on Sunday, June 19. We spent 3 hours discussing things in general. Mrs. Boult took over responsibility for Cutter products from Marie Tatt. She has a 3 person department to handle Bayer and Cutter registration in the U.K.

The next morning, I was taken to the Bayer U.K. office, I met Craig Simpson who is handling Cutter products. Mrs. Glynis Drummond was on holiday and the third position is open. Craig was currently reviewing the rDNA FVIII IND in preparation of the CTX and the Alpha-1-PI PL for submission to DHSS.

1. Koate PL. I told Joyce we should allow the PL to lapse and not renew it since we no longer manufacture non treated Factor VIII.

2. Biotechnology Guidelines. Craig gave me a copy of the 1987 EEC Guidelines for Pharmacy and Clinical Trials. UK will be following these guidelines.

3. Alpha-1-PI. I asked how we go about getting it into the European Pharmacopoeia. Joyce said that if it gets into the BP, it will automatically get into the EP. I will write to the Director, British Pharmacopoeia Commission Secretariat, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ (telephone 1-720-9844/8 ext. GRO-C.

   Craig is preparing the PL for submission and had many questions. (see Attachment 1). I answered them as we went along.

4. DHSS inspection reports. I gave a copy of the responses to both the Berkeley and Clayton inspections and we discussed them.

   a) Clayton

      1) Amending the license to include BPI, Alpha II+III, Paste and Salvage Source Plasma has not yet been done. I explained what all three are. Mrs. Boult is not familiar with plasma products nor is Craig. I briefly went through the Cohn Oncley fractionation scheme - I will send Joyce a copy. I will also send a copy of the current CFR.

      2) The sterilizing cycle which is currently being developed for the freeze drying cycle, needs further

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Elias L. Greene

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detail. (I called Clayton in the afternoon. Phil Wiggins was not there so I spoke with Linda Franke who said the cycle was at 115 degrees C at a calculated Fo of 10).

3) We reviewed the other responses. I explained them as we went along.

b) Berkeley. I went through each response. Duncan Thomas called and interrupted - see below - and we completed the review just before I had to leave. There was so much to cover throughout the day and so little time to do it, we could only do it briefly.

c) Joyce will send me a copy of her response to the DHSS. ✓

5. Koate HS. This PL has been submitted and will go to the July CSM meeting. Mr. John Sloggins of the DHSS, who reviewed it, called Joyce with a number of questions (see Attachment 2).

Answers

1. I will send list of current centers. I explained Short Supply and Cutter's responsibilities for inspection.

2. told her it was USP/BP and is final container pasteurized product.

3. name of hepatitis kit and sensitivity. I told her I do not know what "British Units" were. Our kits are licensed by the FDA.

4. Source of heparin is in QAI; I will supply copy. I will check if USP/BP.

5. Ingredients. What pyrogen test is used, rabbit or LAL? Dose used?

6. PEG. Specification is in QAI. Nominal MW? USP/BP?

7. Prothrombin absorption step - more fully described. Also Al(OH)3 specification. Buffer reagents should be fully specified as to pH, specific conductivity, pyrogens as well as limits.

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8. AHF washing stage has wide range (2-20 degrees C): Explain.

9. Pasteurization step. Concentration of FVIII? Need copy of tracing of temperature during heating cycle. I explained that the inspectors saw ~~show~~ it during their inspection.

10. The stabilizer (sucrose) concentration is different in PLA and published articles. What is the D10 value for HIV in Koate? Article by Levy uses Koate but does not give D10 while McDougal gives D10 but does not use Koate, only tissue culture medium.

11. Why were model viruses chosen, i.e. relationship to hepatitis? I told her our virologist recommended the ones used.

12. He wanted yield information. I told her this was proprietary.

13. Molecular weight cut-off for ultra/diafiltration?

14. Lyophilization - parameters of cycle.

15. Validation of one stage (vs two stage which is in the BP). I told her we have this because all our procedures are validated.

16. Albumin - says we may add. When do we not?

17. Specifications. BP solubility - I showed her we comply. Specifications should reflect batch results (in certificate of analysis). I told her we write PLA as broadly as possible and use in-house QA release to tighten up limits. He wants specific limits for specific activity, iso-agglutinin as per BP, aluminum, reduced limit for fibrinogen and albumin.

18. Identity test should be BP, i.e., FVIII activity as well as human protein.

19. ALT test should be validated. I told her it was and also licensed.

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20. CAE on Koate. There are no limits and no release test, though PLA has it as a test for protein purity. I told her it was only for developmental purposes. Specific activity would reveal extraneous proteins if low.

21. Need stability data for room temperature and full shelf life.

22. Data on batches used in clinical trials.

23. Is supplier of double ended needle approved in UK?

24. Do we intend to sell both HT and HS? I said yes.

25. Moisture control of dry heat process vs. wet heat. I explained both have a limit of NMT 2%. The additional heating after lyophilization is done on a sealed, moisture-proof vial and should not change MOISTURE.

26. Any publications on HS beyond what is in PLA? I do not think so, but will check.

NOTE - Answers should go in by end of week but next week O.K. Joyce will answer what she can and see what Mr. Sloggins says. I explained I would not be back in the office until 1 July.

6. We returned Dr. Thomas' call. He wanted to talk about the hepatitis reports with Koate HT Lot 50S021. I told him we reviewed all the records. Every unit was tested and negative for HBsAg as was the plasma pool. He asked whether we could rule out human error. Of course, we could not. I told him there were unusual features about this incident and only one center had problems, the patients were all old, only in one case could we not find other risk factors, the patients had not been immunized to Hepatitis B even though this is the practice in the U.K. Unlike the previous incident where the pool was positive, the Factor IX made from some of the same pool also resulted in hepatitis; with lot 4 this was not the case. No reports have been received from [redacted]. He asked where else this lot went and I said it only went to U.K. This was because the order

was large enough to include a complete lot. The lot had been released by the FDA.

He asked for a sample of the pool. I told him I would see if any was available. He asked whether we intend to take the product off the market. I said no, because there are patients to whom this product represents no additional risk. We intend and have withdrawn and replaced this lot. I told him we call this a withdrawal rather than recall. He said he had no problem with this. We will probably destroy this lot rather than return it to the U.S. [redacted]

Dr. Trevor Barrowcliffe, who was present at Dr. Thomas', asked for samples of Koate HP and rDNA FVIII. I said I would see if any were available. Dr. Thomas asked whether we intend to sell 3 products when HP is approved. I said probably not but it was not my decision to make.

Dr. Thomas called back later to say he is releasing the lot of Koate HT being held up. For future lots, he wants a sample of plasma pool as we do for Gamimune N. (I called [redacted] Linda Franka and informed her of this requirement).

I asked Joyce to send revised letters to DHSS and NDAB using the word withdrawal in place of recall. She will send us copies of the letter. I will send Joyce a copy of the final report and the FDA letter.

7. Pending future registrations. We ran out of time, so we briefly mentioned:

   a) Koate HP. I will send IND and PLA when available in Sept.

   b) Gamimune N. They are interested in 200 mL size. I told her it might be 250 ml.

[redacted]

8. It may be a good idea if Joyce were to visit Cutter (Berkeley and Clayton) to learn about our products.