To: Dr. M. Sternberg

From: Ralph H. Rousell

Subject: Report of Trip
March 2 - 23, 1986

Ref: JB 86-179

April 14, 1986

copies to:
M. Budinger
M. Collins
W. Ewald
J. P. Fallise
K. Fernandez
M. Fournel
E. Greene
H. Liepmann
C. Patrick
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W. Schaeffler
R. Schwartz
V. Shalson
M. Sternberg
J. Wood

SUMMARY

The purpose of this visit to Europe was to meet and hold discussions with as many of the European investigators involved in studies of Cutter products as possible, to attend the Bayer Medical Directors' meeting, to attend the Bayer International Combined Meeting and dinner, as well as to hold discussions with personnel at Cutter UK involving UK registration of Cutter products, with Jack Wood at Tropon, Cologne to discuss registration in Germany and other European countries, and finally to have discussions with Dr. Vanni and Dr. Cortese at Sclavo covering the registration and promotion of Cutter products in Italy.

IMMUNE GLOBULIN INTRAVENOUS (IGIV)

In the United Kingdom I met with Drs. Joyner and Hegde to discuss their ITP studies. The former has six patients and the latter five patients entered. There have been no problems. Their main concern was over the possibility of HTLV-III transmission.

Also in the United Kingdom, I met with the Scottish Transfusion Group and discussed their plasma fractionation procedures as well as problems associated with AIDS, etc.

In Italy we met with Professor Aiuti, who is doing the registration studies for Sclavo on the new IGIV, pH 4.2.

ALPHA-1 PI

In the United Kingdom I met with Dr. Hutchison and in Germany with Dr. Konietzko. These are two of the foremost European experts in this field. Both physicians strongly advocated that Cutter should perform a controlled clinical study to confirm that the product is effective in arresting the pulmonary deterioration in the PIZZ congenital deficiency patients. They both realized that such a study would take about four years to complete, but felt that it could be accomplished.

KOATE and KONYNE

I left telephone messages for Dr. Kernoff and Dr. Bloom in the UK to invite them to our European rDNA Factor VIII investigators' workshop. I subsequently met with Professor Scharrer of Germany, Professor Allain of France, and Professor Mannucci of Italy and issued similar invitations to them. In general they all felt that they would prefer to have this meeting during the Milan workshop. I agreed that I would discuss this when I returned to the United States. Dr. Allain thanked us for the invitation, but informed me that he would have to refuse as he was taking a position with Abbott in Chicago, U.S.A. commencing April 1, 1986.

I also discussed the ongoing clinical work with the various investigators. Professor Scharrer has only recruited one patient into their Koate-HS study. This patient is in fact a von Willebrands patient and not a hemophilia A. We agreed that the patient should be included. Professor Scharrer presented her in vitro data showing that Koate-HS did contain polymers and was therefore suitable for von Willebrands treatment. However, it did not appear to be quite so marked in the laboratory data as did the Behring preparation. However, clinically, Cutter's Koate-HS corrected the bleeding deficit in the von Willebrands patient.

Dr. Allain in Paris showed us his data on the Koate-HT study. He has had an abstract accepted for the Milan meeting. His conclusion is that while Koate-HT did not entirely prevent non-A non-B infection, the heat-treatment did, however, markedly reduce the infectivity. He also informed me that during 1986 the CNTS expected to import four million units of Autoplex and ten million units of Factor VIII concentrate. He felt that this latter figure might be somewhat higher, even approaching 12 million units.

Dr. Manucci's study on Konyne-HT in Milan in patients with inhibitors to Factor VIII is progressing well. Six patients have been included with satisfactory results.

GENERAL

Throughout this trip I was accompanied by Dr. J. P. Fallise, Cutter Medical Monitor for Europe. This was arranged to emphasize Cutter U.S.A. support for Dr. Fallise and also, where appropriate, to introduce Dr. Fallise to investigators whom he had not met before but who were known to Dr. R. H. Rousell.

GRO-C

BC112407

UNITED KINGDOM, MARCH 3 TO 7, 1986
Dr. D. Hutchison,
Kings' College Hospital,
Denmark Hill, London

ACTION/INFORMATION

TRIP REPORT

Dr. Hutchison is interested in performing studies of Alpha-1 PI in the United Kingdom. He is the coordinator/ secretary of the British Thoracic Society's Register of Alpha-1 Antitrypsin Deficiency Patients in the UK. He therefore has access to all such patients in the UK.

He is interested in two possible studies:

1. A study on the use of alpha-1 in the post-surgical management of patients receiving heart-lung transplant for gross respiratory impairment caused by alpha-1 antitrypsin deficiency. Apparently at the present time Dr. Hutchison has two patients whom he feels should receive heart-lung transplants. However the surgeons are unwilling to embark upon such a procedure without the promise of alpha-1 PI substitution therapy in the post-surgical period. I promised Dr. Hutchison that we would get back to him on this particular proposal in the third quarter of1986, once we had had the opportunity to assess our commitments to the congenital deficiency studies. I did not encourage him that we would be able to collaborate.

R.H. Rousell/R.S. Schwartz

BC112408

ACTION/INFORMATION

TRIP REPORT

(NOTE: In subsequent discussions with Dr. Crystal, of the NIH in the U.S.A., Dr. Crystal felt that usage would not achieve much. He felt that post-surgical complications would be very unlikely to be mediated through overactivity of elastase. He therefore considered that an elastase inhibitor would do very little for the patients. If alpha-1 PI is likely to be of benefit in such cases, then it would also be of benefit in ARDS. We should perform any ARDS studies first, before embarking upon studies such as heart/lung transplant where the data would be extremely difficult to interpret.)

2. A controlled study on the efficacy of alpha-1 PI augmentation in reducing the deterioration in pulmonary function of patients with PiZZ alpha-1 antitrypsin deficiency. Dr. Hutchison has prepared a paper on this subject (copy was supplied). This paper is being submitted for publication. He has estimated that there would be a reasonable chance of obtaining a statistically significant result in a study involving 80 patients (40 treated and 40 controls) studied over a period of four years. He feels that such a study could be undertaken on an international multicenter basis. I promised that we would discuss his proposition at Cutter and we would come back to him with an answer early in 1987.

R. H. Rousell/R. Schwartz/
J. P. Fallise

BC112409

DISCUSSIONS AT MILES UK
Stoke Court, Stoke Poges

Participants: Dr. B. Elliott, Miles; Mr. B. Dyos, Cutter UK; Marie Tatt, Cutter UK; Linda Frith, Cutter UK; Dr. J. P. Fallise, Cutter Europe; and Dr. R. H. Rousell, Cutter U.S.A.

ACTION/INFORMATION

TRIP REPORT

At the request of Dr. Greene, we discussed the text of the Cutter UK response to the Committee on the Safety of Medicines' inquiries concerning the Konyne-HT product license application. Cutter UK will be responding in writing and will apply for a verbal hearing at the CSM as well.

We also discussed the response of Cutter UK to the Department of Health and Social Security who had queried the recall in the United States of a number of lots of Koate-HT with the concern that one of the lots involved had also been distributed in the UK and had not been recalled. It had been possible to present all the relevant documents to the DHSS and demonstrate that Cutter had acted in a very swift and responsible manner and that the report which the DHSS had seen was in fact not quite correct.

Cutter UK also reported on the possible transmission of hepatitis B in patients receiving Konyne lot 20N028. Apparently six hemophilia B patients were treated by Dr. Mitchell at the Leicester Royal Infirmary. Three of these patients were immune to hepatitis B, as evidenced by having HBsAb levels prior to the Konyne-HT therapy. The other three were in fact negative. Of the negative patients, one child has now developed clinical hepatitis B. This child had been tested in June and August, 1985, and was HBsAg negative.

ACTION/INFORMATION	TRIP REPORT
K. Fernandez	Tested again in February, 1986, this child was confirmed to be HBsAg positive. Of the other two children, one has been transferred to Sheffield. This case will be followed up. The test results for hepatitis B surface antigen were not yet available in the third case. We will be informed of their follow-up. We discussed the general progress of the clinical studies in the United States. Cutter UK were also informed of the rDNA Factor VIII investigators' meeting proposed for June, 1986 (this date has now been rescheduled to 23rd September, 1986). They were informed that Dr. P. Kernoff of the Royal Free Hospital of London and Dr. Bloom of Cardiff Royal Infirmary would be invited to this meeting.

VISIT TO DR. P.L. YAP AND DR. B. McCLELLAND
Edinburgh and Southeast Scotland
Blood Transfusion Service
Edinburgh, Scotland

Participants: Dr. P. L. Yap, Dr. B. McClelland, Dr. J. P. Fallise, Dr. R. H. Rousell.

Discussions centered around the studies being done in the United Kingdom on intravenous immune globulins and the work that Cutter was doing. They are extremely interested in our data on the non-transmission of HTLV-III by intravenous immune globulin.

BC112411

ACTION/INFORMATION	TRIP REPORT
Dr. R. H. Rousell	Dr. Yap informed us of the work by Dr. Webster, namely that one of his patients with a myeloma had developed common variable immune deficiency. Apparently the patient was given Sandoz IGIV and they were able to isolate a retrovirus from the patient. Dr. Webster feels that common variable immune deficiency is caused by a virus and hence his attempts to isolate a retrovirus from these patients. Apparently he will publish his "findings". Dr. Webster's paper has subsequently been published in the Lancet and we have drafted a reply.
Dr. R. H. Rousell	Dr. Yap also referred us to the proceedings of the Royal Society of Medicine issue # 84 in their International Congress and Symposium series. This particular issue was devoted to intravenous immune globulins in immune deficiency and ITPs. He recommended that we obtain copies and supplied a copy to Dr. Fallise. We promised to also send a copy of the paper by Dr. Ayre Rubinstein on the treatment of AIDS in children to Dr. Yap.
Dr. R. H. Rousell	Dr. Yap also informed us that Sandoz had been manufacturing the Burroughs-Wellcome Pseudomonas Vaccine to hyper-immunize their donors. In their experience, Burroughs-Wellcome gave good levels of antibodies against the O antigen. However, in general their other antibodies were not of significance. Apparently Dr. Yap has been informed that Sandoz are no longer hyperimmunizing their donors.

ACTION/INFORMATION **TRIP REPORT**

Dr. Yap recommended that if we wish to receive supplies of Burroughs-Wellcome Pseudomonas Vaccine, we should write to Dr. Peter Hambleton or Professor Jack Mellings in the Department of Vaccine Production at Burroughs-Wellcome, Porton Downs, Salisbury, Wiltshire, England.

M. Collins

Dr. McClelland and Dr. Yap are investigating Pseudomonas monoclonals. They have a technique in which they are able to assess binding to effector cells. They are interested in assessing Cutter preparations. We mentioned that Mike Collins may be visiting Germany (Tubingen in June/July) It was suggested that he visit this group in Scotland. I promised to inform Dr. Collins. Dr. Yap's number in Edinburgh is 031-229-7291.

M. Collins

Dr. Yap supplied us with copies of the Southeast Scotland Transfusion Service information leaflets on blood donation and AIDS as well as their check list for assessing the health of blood donors. These will be supplied to Sunil Bhonsle.

Sunil Bhonsle

VISIT TO DR. MILES JOYNER
Royal Devon and Exeter Hospital
Clinical Study on ITP

This is one of the two centers involved in our UK ITP studies. They had no major concerns. They have included six patients with reasonable results to date. They will admit a further four to nine patients. We discussed the safety of IGIV, pH 4.2 as regards non-transmission of HTLV-III. They are also including pregnant patients in their study.

BC112413

VISIT TO DR. UDAY HEGDE
Ealing Hospital, London
Investigator on IGIV, pH 4.2
in ITP

ACTION/INFORMATION

R. H. Rousell

TRIP REPORT

This is the second of the two centers involved in our UK ITP study. They have completed five of the approximate 15 patients to be admitted.

They did have concerns about the transmission of HTLV-III by intravenous immune globulin. I was able to show them our experimental and clinical data and reassure Dr. Hegde on this basis. I promised to send him copies of the appropriate publications as soon as they were ready.

Dr. Hegde is a leading figure in British Medical circles on the treatment of ITP and has published a rather large number of papers in this context. He has also published on the management of ITP during pregnancy and they will be using our IGIV for such cases.

These two centers anticipate study completion later this year and then will publish the results.

ATTENDANCE AT THE BAYER'S MEDICAL DIRECTORS' MEETING
March 9 & 10, 1986
Aachen, West Germany

ACTION/INFORMATION

TRIP REPORT

The meeting was attended by the medical directors of Spain. U.S.A., South Africa, France, Australia, Germany, Canada, Venezuela, the Netherlands, Italy, Japan, Germany, Sweden, and the United Kingdom. Participants from the U.S.A. included Dr. Allen, representing the Medical Department of Miles Westhaven, myself, representing the Medical Department of Cutter Biological, and Dr. Spiekermann, who has overall responsibility for Bayer Clinical Research in North America. The meeting was recorded and complete details are available in the minutes issued by Dr. D. Suwelack, Department of Overseas Administration. Additional informational copies of specific items will be supplied on request. Only the highlights of the meeting with special relevance to Cutter will be presented in this report.

Professor Krebs chaired the meeting and opened the program (see Addendum 1. for the agenda). Professor Krebs will leave the Department of Research and Development at the end of May for Italy. His successor will be Professor Hoffmeister. Professor Weihrauch takes over the responsibility for the Medical Department. One of Professor Weihrauch's Department heads is Dr. Baumann, who is in charge of Clinical Research Section II, as well as coordinator for Bayer clinical trials in South America. Dr. Fallise, who does Cutter studies in Europe reports to Dr. Baumann.

ACTION/INFORMATION

TRIP REPORT

Professor Krebs gave an overview of the allocation of financial and manpower resources in the various research fields within the healthcare sector. He stressed Bayer's commitment to new technologies and emphasized Cutter's place in this hierarchy. He did, however, indicate that it was Bayer's intention to hold the R&D in the biological fields at its present level in the long-term plan. He also presented a very informative explanation on the costs of introducing a new chemical entity (NCE) and the time taken to reach break-even point (Appendix 3). The average new chemical entity will only reach the break-even point some 24 years after commencement of R&D. This is usually some 12 years after market introduction. Many new chemical entities never reach a break-even point. In conclusion, since projects with annual sales of about $9,000,000 will only reach break-even in 24 years, for a new chemical entity to be profitable, it should achieve sales of in excess of $50,000,000 annually. Only about 3% of NCE's achieve this target.

He also mentioned that all pharmaceuticals are gradually changing from their current areas of research to life sciences, which are rather innovative. He went on to indicate that by 1990, the intention was that discovery biological research, for example genetically engineered products, would be transferred from Wuppertal and Berkeley to Westhaven. However, developmental research would remain as they are at present. In 1988, for example, Westhaven would be including research on HTLV-III, etc. He also dealt with the centralization of toxicology departments at one center.

ACTION/INFORMATION

TRIP REPORT

Professor Weihrauch presented the way a new development project is handled in Bayer R&D (Appendix 4). This method has confirmed good results with eight different compounds now.

Other items included the status of registration of various new compounds in Germany, the result of the last continent coordination meeting, the results of the medical information meeting, the concept of a medical directors' newsletter, the scope of Phase IV clinical studies (Appendix 5), the standardization of Bayer package inserts on an international basis (Appendix 6), the international study register and the application to Bayer for clinical trials, distribution of Bayer clinical supplies, and Bayer's need for an international biometric system.

The concept of an international biometric system is of interest to Cutter, especially in view of the fact that we are now being requested to analyze data obtained by Tropon in their clinical studies of Cutter products.

Following these presentations, the medical directors, including myself, presented the organization, achievements, and projections of their various departments in the different countries.

In conclusion it was decided that it would be necessary for Bayer to hold a medical directors' meeting every six months. Accordingly, the next medical directors' meeting will be held on October 20-21, 1986 in Milan, Italy.

ADDITIONAL NOTES

ACTION/INFORMATION TRIP REPORT

1. Bayer absolutely forbids "seeding" operations where a clinician is paid money to use the drug in question. These are absolutely unethical. Phase IV studies must be properly designed, monitored, evaluated, and reported upon. The medical director in each appropriate country takes the responsibility for Bayer (this includes Miles', Cutter's, etc. drugs being used under a clinical trial umbrella. If this is contravened, it is the duty of the Medical Director to report this directly to Bayer.

2. Bayer has entirely eliminated "emergency" requests for clinical trial supplies. This means that overseas subsidiaries must budget for their clinical trial needs and inform Bayer well in advance. Bayer will not under any circumstances change their schedules because of inefficient planning for clinical studies.

DISCUSSIONS WITH J. WOOD
March 11, 1986
Participants: Dr. J. P. Fallise, J. Wood, R.H. Rousell

1. It was agreed that Professor Robert, who is investigating methods for assaying elastin degradation products which will contribute to our alpha-1 antitrypsin program, would be paid by Bayer France. This had been confirmed to me previously by Dr. Griener of Bayer France.

M. Fournel

ACTION/INFORMATION **TRIP REPORT**

2. It was agreed with Jack Wood that Cutter Clinical Research would send our alpha-1 PI clinical report to Dr. J. P. Fallise as soon as it is ready. This would be followed by the entire PLA package at the end of April.

R. Schwartz/H. Liepmann

3. Coagulation clinical studies in Italy. These were discussed and the following items were agreed:

   a. The Koate-HT results in virgin hemophilics developed by Professor Mancuso (Palermo), Professor Biddau (Cagliari), and Professor Rodighiero (Vicenza) might best be published in a journal such as Vox Sanguinis. It was agreed that if this group or Dr. Cortese of Sclavo could develop a draft manuscript, Dr. Rousell would be happy to review this and make appropriate suggestions for grammatical changes.

J. Wood and Dr. Fallise

   b. Professor Mariani (Rome) study on the various factor IX products could not be funded by Cutter.

   c. The proposed study by Professor Carnelli (Milan) of factor VIII in virgin hemophilia A patients could be supported in late 1986 using Koate-HS. In the light of recent events, this could well be advanced (see discussions with Sclavo).

J.P. Fallise/R.H. Rousell

   Cutter could agree to supply product only for this study, but Sclavo would have to provide the honoraria.

   d. It was confirmed that Cutter would be funding the study of IGIV,pH 4.2 by Professor Ugazio in Rome in leukemic children (50 million lire), and by Professor Aiuti in Rome on the prophylaxis of infection in patients undergoing surgical procedures.

ACTION/INFORMATION **TRIP REPORT**

e. It was also agreed that we would not be able to fund the IGIV, pH 4.2 ITP studies by Professor Carnelli in Milan or Professor Vierucci in Florence as these were studies of interest solely to the Italian market and did not have any international implications.

J. Wood/R.H. Rousell/
J.P. Fallise/H. Liepmann

4. Invoicing for the costs incurred by the Cutter Clinical Monitor in Europe.

There appears to be some confusion which has arisen as to what percentage of what expenses would be paid by Cutter and what would be funded by Bayer. It was agreed that Dr. Rousell would discuss this with Dr. Brandau (due to time constraints, it was not possible to discuss this with Dr. Brandau, except to mention it briefly. Dr. Rousell therefore agreed with Dr. Brandau that he would draw up a definitive document on the subject and send this to Dr. Brandau).

GRO-C

R.H. Rousell

It was stressed that Cutter would like to adhere to the original agreement as worked out between J. Wood and Professor Krebs, namely that Bayer would fund the salary and expenses for the secretary, the secretarial office, the medical monitor's office, and other overheads, etc., and in addition would absorb 20% of the costs for the medical monitor including salary overheads, travel, etc., etc., as well as 20% of the clinical research costs (study honoraria and trial supplies). Dr. Rousell will write to Dr. Brandau to obtain clarification.

R.H. Rousell

BC112420

ACTION/INFORMATION **TRIP REPORT**

5. It was agreed that Cutter U.S.A. would send our alpha-1 PI clinical report to Dr. Fallise as soon as it is ready to enable him to commence working on the German submission. The PLA will be sent to Dr. Fallise at a slightly later stage.

R.S. Schwartz/E. Greene/
R.H. Rousell

MEETING WITH PROFESSOR DR. N. KONIETZKO,
Investigator for Alpha-1 PI,
Essen, March 12, 1986

Dr. Fallise and I visited Professor Konietzko at the Ruhrland Hospital in Essen. This is a specialized hospital dealing only with diseases of the chest. It is probably a former TB hospital. Apparently Professor Konietzko has now been made director of the entire hospital in addition to his position as head internal medicine.

We discussed the reasons behind offering active immunization against hepatitis B to all patients involved in our initial studies. I feel we were able to satisfy Professor Konietzko that such immunization was merely a precaution and that there was very little or even no risk of transmission of hepatitis B. The study is progressing extremely smoothly. Professor Konietzko has had to drop one patient from his group of nine patient. The reason was that the patient concerned had not refrained from smoking and Professor Konietzko feels that alpha-1 PI concentrate should not be administered to any individual who is not prepared to take the elementary precautions against making his disease worse.

Ralph
Were you able to eliminate Hep B Vaccination?
Sure would help our mktg

GRO-C

ACTION/INFORMATION TRIP REPORT

He is also very much in favor of a controlled clinical study. He agrees with Dr. Hutchison in the United Kingdom. He would be willing to collaborate in an international multicenter study. He feels that once the product is licensed, there is a very strong possibility that it would be used in an inappropriate manner, especially in the private sector. He feels that only a controlled clinical study confirming efficacy in specified patient populations would guarantee health insurance reimbursement.

We promised to keep Professor Konietzko informed regarding the situation concerning possible transmission of hepatitis B. We also promised that we would keep him informed on any progress concerning the development of a controlled study, especially on an international basis.

J.P. Fallise/
R.H.Rousell/R. Schwartz/
M. Sternberg

DISCUSSIONS WITH PROFESSOR J. P. ALLAIN
Centre National de Transfusion Sanguine,
Paris. March 13, 1986

Dr. Fallise and I met Professor Allain at the CNTS offices in Paris. We covered the following items:

1. Participation in the Cutter European rDNA workshop. Professor Allain mentioned that he was extremely interested in this project, however he would regretfully have to refuse our invitation as he has resigned from the CNTS and will be taking a position with Abbott in Chicago commencing April 1, 1986. His agreement with the CNTS precludes him from working in the hemophilia area for probably another year. At Abbott he will be dealing with the diagnostic kits for AIDS, etc.

BC112422

ACTION/INFORMATION **TRIP REPORT**

I reaffirmed our invitation to Professor Allain to visit Cutter and deliver a seminar.

2. Professor Allain confirmed that he will be attending the Milan hemophilia meeting in June and will be presenting the data on his study involving Koate-HT. He confirmed that none of the 11 patients investigated had developed LAV antibodies. Of his 11 patients, six had never been exposed to blood products, while five were so-called "liver virgins." Of the six previously unexposed patients, only one developed a moderate elevation of ALT suggestive of non-A non-B. Professor Allain's conclusion is that Koate-HT carries no risk of transmission of LAV and a very low risk of transmitting non-A non-B viruses.

3. Professor Allain is impressed with the immuno-steam-heat treatment for Factor VIII and Factor IX. Apparently the CNTS has performed a pilot study and is now undertaking a definitive study with a steam-heated factor IX preparation. I rather gathered that this was a CNTS product prepared according to the Immuno specs. Professor Allain feels that it is as good as the wet heat treated factor VIII of Behringwerke.

4. They have also investigated the activity of the heat-treated factor IX preparations in controlling bleeding in hemophilia A patients with inhibitors. Their results are in keeping with those previously reported by Lusher et al. Professor Allain feels that there is excessive use of the so-called "activated" preparations in France to control bleeding in the inhibitor patients. He would prefer to see the factor IX preparations tried before resorting to the very expensive activated preparations.

Koate HT

BC112423

ACTION/INFORMATION TRIP REPORT

5. He confirmed that there would be approximately four million units of Autoplex ordered by the CNTS in 1986, and that they estimated that there would be 10 million units of commercial factor VIII imported into France. He feels, however, that this figure of 10 million units may well be too low and the final figure may reach 12 million units.

J. Wood/P. DeHart

MEETING WITH PROFESSOR SCHARRER
Clinical investigator Koate-HS,
Frankfurt. March 14, 1986
Participants: Professor Scharrer,
Dr. R. Neumann, Mr. Knebel
(Tropon's area manager), and
Dr. R.H. Rousell

The discussions revolved around the progress of Professor Scharrer's study of Koate-HS in virgin hemophilics. To date they have been unable to recruit any virgin hemophilics, but there is one suitable von Willebrands patient. It was agreed that this patient could be entered into the study. Professor Scharrer confirmed that the Cutter Koate-HS had corrected the coagulation deficit in the von Willebrands patient. After infusion of Koate-HS, the bleeding time in the patient was restored to normal.

Professor Scharrer also showed us her <u>in vitro</u> work comparing Koate-HS with Behringwerke factor VIII-HS. She showed that the low- and medium-molecular weight multimers were present in reasonable concentrations in Koate-HS and that there was a low concentration of the higher molecular weight multimers. The Behringwerke preparation on the other hand had more high molecular weight multimers.

ACTION/INFORMATION **TRIP REPORT**

She would like to assess another lot of Koate-HS to see if there is variation from lot to lot and whether the Cutter preparation is similar to the Behringwerke preparation.

She also mentioned that Dr. Lou Aledort is convening a von Willebrands meeting after the Milan Conference. She therefore would not be able to attend the Cutter rDNA Factor VIII Workshop if it were held immediately after the Milan Conference or immediately before the conference. She would prefer the meeting to be held during the Milan Conference.

Professor Scharrer confirmed that she also has both congenital AT-III deficient and congenital Protein C deficient patients under her care.

J.P. Fallise/R.S. Schwartz

Her patient population includes about 850 patients under 45 years of age with a variety of coagulation defects, including an AT-III deficiency, Protein C deficieny, plasminogen activator release deficiency, etc. She is interested in discussing studies in this area as well.

DISCUSSIONS WITH PROFESSOR P.M. MANUCCI
Hemophilia and Thrombosis Center
University of Milan, Milan Italy
March 17, 1986

Dr. Fallise and I met with the Medical Director of Sclavo, Dr. U. Cortese, and visited Professor Manucci in his clinic.

ACTION/INFORMATION TRIP REPORT

Professor Manucci is extremely involved in the forthcoming hemophilia meeting in Milan. We discussed the results of his study using Konyne-HT to treat hemorrhages in hemophilia A patients with inhibitors. The protocol, of course, calls for the treatment of 30 bleeding episodes. To date six episodes have been treated in six different patients. Four of the patients responded in a satisfactory manner. We discussed that these results were very much in keeping with what we had heard from Professor Allain and also our own experiences in the United States. Professor Manucci is also very much of the opinion that there is far too excessive use of the activated factor IX preparations for patients with inhibitors.

Regarding the Cutter workshop on rDNA Factor VIII, Professor Manucci also was very pleased to accept our invitation to attend and participate in the workshop, however, he would be unable to attend either before or after the Milan meeting, and would prefer it if the workshop would be held during the meeting or at some other time. We promised to keep him informed.

MEETING WITH PROFESSOR FERNANDO AIUTI
Department of Clinical Allergy and Immunology
Universita degli Studi di Roma "La Sapienza"
Rome, Italy. March 18, 1986

Our studies on IGIV, pH 4.2 for licensing will be conducted by Professor Aiuti. Dr. Cortese, Dr. Fallise and I visited him. Professor Aiuti recalled the last meeting which I had with him. This was in Kyoto, Japan, at the last World Immunology meeting when we had been introduced by Dr. Bob Good.

ACTION/INFORMATION **TRIP REPORT**

Supplies forProfessor Aiuti's surgical study had just arrived at Sclavo and the study should be commencing fairly soon. There were no outstanding problems. Professor Aiuti felt also that it would be necessary to perform a small study of two infusions of IGIV, pH 4.2 in about ten immune deficient patients in order to satisfy the regulatory authorities in Italy as to the safety of the preparation. We agreed to discuss this and Professor Aiuti will be making a formal approach to Dr. Cortese.

J. Wood/J.P. Fallise

We also discussed possible passive transfer of hyper-sensitivity by the use of gammaglobulin concentrates. Professor Aiuti has done a great deal of work in this area and very kindly supplied me with a selection of reprints on his work. These will be of especial interest to Dr. Rebecca Buckley in the United States. One of the papers has just been accepted for publication and is in the printer's proof stage. I asked Professor Aiuti specifically if he could forward a copy to Dr. Buckley and he agreed that this was in order.

M. Budinger/
R. H. Rousell

We finally made a tour of their facilities. It was conducted by Professor Aiuti. They are certainly undertaking a great deal of interesting work there and do have a very highly organized and productive department.

DISCUSSIONS AT SCLAVO
March 19, 1986

Dr. Fallise and I met with Dr. Vanni, Dr. Podda, and Dr. Ciccarese in Dr. Cortese's department. The following items were covered:

ACTION/INFORMATION **TRIP REPORT**

1. Dr. Podda requested that we supply him with a copy of the IGIV, pH 4.2 U.S.A. letter of approval from the FDA. He also requested supplies for QA testing as soon as possible and stressed that to make this product a success in Italy they urgently require publications. done

E. Greene/R.H. Rousell/
H. Liepmann/

2. Dr. Vanni reimphasized Dr. Cortese's statement that they needed 200 x 50 ml vials IGIV, pH 4.2 for registration. 100 of these would be for the registration, and 100 vials would be for seeding samples. They felt that in June they would require another 100 samples for customers. done

3. Dr. Vanni requested in addition any publications that we could supply. He would be happy to receive articles from us and would arrange the translation into Italian and publication in an Italian journal. done

R.H. Rousell

4. Dr. Vanni stated that the sales of IGIV in Italy were very good and that he felt that publications would assist them in increasing their market share. They are hoping to launch IGIV, pH 4.2 in early 1987.

Bill What above since? GRO-C

5. They requested about 50 copies each of all U.S.A. promotional material, including the information booklet.

H. Liepmann/W. Dever

6. They will have the same price for IGIV, pH 4.2 as they do for the current IGIV, pH 6.8 (IGVENA). There license application will be a reformulation submission, but they do feel that in spite of this, the time for registration will be roughly one year.

through my office pls.

BC112428

ACTION/INFORMATION **TRIP REPORT**

7. The proposed study of Koate-HS by Professor Carnelli was discussed. Apparently a group of pediatric hematologists in Italy are forming a satellite group to the world hemophilia congress. They would be interested in investigating Koate-HS. It was discussed as to whether they may prefer to wait for the rDNA factor VIII, as Professor Manucci would be starting studies on the rDNA factor VIII in early 1987. It was agreed that we could discuss this with J. Wood. (Since the meeting at Sclavo, emphasis been placed upon Koate-HS studies and it seems therefore that we should make strong recommendations to Sclavo that Professor Carnelli's study with Koate-HS is agreed upon and implemented as soon as possible. Dr. Fallise will have to do this. We will send Dr. Fallise a copy of Professor Scharrer's protocol from the U.S.A.

J. Wood/J.P. Fallise/ R.H. Rousell/H. Liepmann

Go slow

8. Sclavo is also interested in a large world multicenter study of IGIV, pH 4.2 in ITP. They would like Cutter to subsidize the supplies for the study and they would agree to pay the honoraria. It was agreed that this would be discussed, but it was also stressed that we had accumulated a great deal of data in ITP and that the indication was proved by the FDA and therefore generally accepted. It might be that such additional studies are only of interest to Sclavo for use in Italy. It was again confirmed that we would discuss Sclavo's proposal and get back to them with a definite comment.

J. Wood/J.P. Fallise/ R.H. Rousell/H. Liepmann

RALPH Who? For Jane? After our [illegible] meeting?

RHR:jb

GRO-C

GRO-C

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