CUTTER INTERNATIONAL

MANAGERS' MEETING

Blood Products Industry in the U.S. and internationally

J. N. Ashworth

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One of the big advantages of a get-together like this is for each of us to talk about his own area of work so that the rest of us can learn something and perhaps can understand the intricacies of the problems that face each of us. We each try to fill our niche in the organization completely so that the combination of our efforts constitutes the entire job of the International Group. The agenda for this meeting, I think fulfills the objective for me. I shall learn what each of you feels is his field of contribution, what you feel are your challenges, what you feel you can accomplish and perhaps how I and others can help you. Since I had nothing to do with the agenda preparation, I believe I can start everything on a note of congratulations to the framers of our week's work and toast to the success of our endeavors in the words of my old friend Cadberry who said "May the best of this year be the worst of next".

On that happy promising note, I would like to try this morning to contribute my offering of information in the form of a tour, somewhat abbreviated, but I hope not too cryptic or succinct. This will be a tour of some facets of blood and plasma in the U.S. and in the rest of the world, in the hope that I can create a basis for a developing perspective of what the world of blood and plasma may be coming to. From this perspective, if we all share in it through my efforts this morning, it could be easier, in the coming months and years, for us to plan Cutter's future in blood and plasma from some of the same knowledge base.

Thus I would like to borrow a little from a previous discussion on this that I gave two and a half years ago and expand and bring up to date the information.

Though I have written most of this out, as you've noticed, so that there's a better chance of having it organized reasonably well, I implore you to yell at any moment to question my thesis or add your own comments to enlarge on my presentation. This is not a speech; it's a led discussion. So I welcome your participation. My learned colleagues, like Lowell and Carroll particularly, may yawn and nod a little at my exposition on matters with which they are quite familiar, so stay awake fellows and see if you can detect the purposely inserted error. One drink on me for each of you for catching it.

Do I need to say to you that there are many individuals and organizations contributing to the complexity of the blood and plasma scene. There are so many that it is difficult for one person to keep track and to insure authoritative participation in the various forums taking place on the subject and thus to assist in the formulation by Cutter of policies designed to keep us on top of the situation. Cutter's destiny and profits for a

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significant slice of its business will be determined by the wisdom of those policies.

To start first with the domestic situation may be wise, since, as many of you know, the rest of the world has significant dependence on the U.S. for supplies of plasma products. Like the Middle East countries and the oil supply, future events in the U.S. have potential for causing not gasoline lines elsewhere but albumin lines, AHF lines and plasma lines. Many don't understand that this may well be true.

In the U.S. the most coordinated program in whole blood is the U.S. American National Red Cross. It operates 58 centers under central administration and technical control and last year collected about 5 million units of blood out of a U.S. total of 12 million. Most of all its centers prepare and supply a full line of components such as packed red cells, platelets, cryo-precipitate and in addition send plasma, either fresh frozen or otherwise outdated or ind.ated but from whole blood for fractionation under contract with either Hyland, Armour or Cutter. At about 500,000 liters per year, this is about 10-15% of the plasma fractionated in the U.S. Just for fun I'd like to say that, in early 1952, 27 years ago, I participated in setting up the first Red Cross Contract for fractionation of RC plasma. It was with Cutter. My first year's plasma supply was about 35,000 liters. So there has been some growth since. The contract basis has remained essentially unchanged since. But now, finally, Red Cross has decided it wants to do its own and has signed a fascinatingly intriguing contract with Hyland to build a fractionation plant in a joint venture called Fractionation Associates with a one million liter a year capacity. Land has been acquired almost within hailing distance of Cutter's Clayton, North Carolina, plant. We now await the next steps. The 64,000 dollar question is how many Clayton people will they hire away. Us old Baxter-Travenol-Hylanders here, and back home look with some amazement and wonderment at this venture particularly in view of the serious management and technical difficulties Hyland has been having. Tune in next year for a progress report.

On to more blood bankers. The American Association of Blood Banks is a trade organization of about 2000 institutional members (that is, various kinds of blood banks) and about 5000 individual members. The institutional members have the vote on AABB policies. The institutional members remain autonomous but, under the umbrella of the AABB, they cooperate in standardizing by means of various publications written by many committees. The technical procedures of the AABB have widespread utilization as authoritative documents by other blood bankers and these manuals of procedures are accorded recognition by the FDA as acceptable procedures in the case of inspections. The AABB members account for 5 million or so units of blood collected in the U.S. Because they are a heterogeneous group, their blood services vary widely depending on the size and needs of the medical community served.

Another maverick group of blood banks, formed because of philosophical differences, is a band of, I think, 13 AABB dissidents such as the enormous New York Blood Center and Blood Services (headquarters located in Phoenix with approximately 23 centers in the central U.S.)

These CCBC blood bankers advocate policies sometimes only subtly different from that of the Red Cross hierarchy. Their principal difference in point of view with the AABB people is probably over the so-called penalty fee or responsibility fee which, after some semantic laundering, is now usually called a non-replacement fee. I think I will mention a little more about this later.

The CCBC like the Red Cross embraces the idea that the community should be responsible rather than individuals for blood supplies.

The American Blood Resources Association started perhaps ten years ago as a group of whole blood banks operating on a commercial basis or if you will, profit makers. With advancing pressures to get rid of these onerous commercial whole blood bankers, their ranks have thinned and the ABRA is now mostly a trade association of the 200 or so independently operated plasmapheresis centers. For many years ABRA was fairly strident and perhaps somewhat radical in its voice and thus Cutter and the other fractionators did not chose to be members of the organization. Lately ABRA has toned down its stidency and is beginning to play a quite responsible role in advocating the proper recognition and need for plasmapheresis. One or two fractionators have joined. Alpha for one. They have sponsored two very useful Plasma Forums, meetings at which they have been very successful in bringing all sides of the blood and plasma picture together for useful, non-emotional discussion of the important issues. Cutter sponsored the publication of the proceedings of the first Plasma Forum.

The remaining group of blood or plasma processors is of course the fractionators. In the United States the four big ones are Cutter, Hyland, Armour and Alpha. Others are Merck Sharp & Dohme, Parke-Davis, Merieux and Michigan. Each of the fractionators has of necessity become involved itself in the collection of plasma and each own from 10 to 20 pheresis centers. Cutter utilizes the output of about 100 centers and I think at latest count we own 20 of them. There are about 275 centers in the U.S. that are licensed to produce Source Plasma (Human), which is the proper name assigned by the FDA for the plasma collected by plasmapheresis and used as the principal starting material for the preparation of fractions. We are restricted in our raw material to plasma from plasmapheresis centers or blood banks licensed or otherwise registered by the U.S. FDA. There are none licensed outside the U.S. The last one was in Nicaragua. The turmoil down there 2 or 3 years ago resulted in the burning of this center. When I mentioned that we get plasma from blood banks, I was referring to about 10% of our input. This is plasma derived from whole blood which has either gone outdated or has been used for the preparation of components such as packed cells. For completeness I should also mention that some of the output of pheresis centers and blood banks goes to the manufacture of clinical laboratories. The coagulation lab products that Lowell will discuss later are examples of these. My experience in the manufacturing of these products is a little distant now but I may not be far off in estimating that 1.5 million liters per year are used for these products. It is not an insignificant part of the business utilizing human plasma.

The last participant on the national scene in this can of worms we are living with is the Bureau of Biologics. This is the agency in the FDA that administers the laws pertaining to blood and plasma. I hope you will excuse the strength of expression of my ideas but I know many agree with me when I say that it is more of a pain in the neck every day through its overzealous interpretation of its mandate in administering the provisions of the Federal Food and Drug and Cosmetic Act and more particularly the biological products provisions of the Public Health Service Act. The Bureau is our most frustrating problem.

I would like now to mention a few of the conflicts that make the blood and plasma scene a difficult situation in which to obtain any unanimity on policy. I mentioned before the issue of whether or not the supply of blood is primarily the responsibility of the community and its citizens to donate without regard for a specific patient's needs but only to keep the bank full. This is the way the Red Cross and the CCBC think. The voice on the other side is that of the AABB whose members feel equally strongly that donor recruitment should be tied much more specifically into responsibilities related to each patient's needs. There does not seem to be any way to compromise these two positions. This has led to an open battle between the Red Cross and the AABB that continues to be the subject of much rhetoric and publication in blood banking related journals and often in the public press.

A spin-off of this controversy concerns the non-replacement fee. This fee or charge is assessed if blood used is not replaced. The Red Cross will have nothing to do with this but the AABB argues that it is a powerful tool in donor motivation.

Then there is the issue which is perhaps the most ridiculous. The highly emotional volunteer donor versus paid donor controversy has wasted more time than it is worth. Most of this derives from the basic danger of transmission of hepatitis. Studies were done supposedly with proper selection of controls which have purported to show that the incidence of hepatitis from blood or its components from donors who had received payment is significantly higher. I won't spend time relating many of the ridiculous and irrelevant issues that have been raised in the course of this controversy. If it were not such a serious issue I think it might be possible to laugh at some of the things that have been done and said. Nevertheless, we ended up having the BoB pontificate a definition of a paid donor and as you can imagine, some of the interpretations of this are peculiar. Apparently one is <u>not</u> a paid donor if one gets a day off from work for giving blood but you <u>are</u> a paid donor if you get a merchandise certificate for some item donated by a well-meaning store. This last issue of the differentiation between a volunteer and a paid donor has worldwide ramifications also, but more on morality grounds than on safety grounds.

Now we're not going to let the U.S. Government off easy as a participant in this situation. In addition to the BoB there has been a program for about 7 years that was hatched by the initial argument about volunteer vs paid donors and the resulting questions on the safety of

blood. At that time, almost in self-defense, the Department of Health, Education and Welfare, in anticipation of possible congressional action, formulated a national policy which has turned out to be one of the more useless documents that has come out of a government agency, although some of you may have examples of your own to put up against it. An objective of the national blood policy is or was the attainment of peaceful and cooperative coexistence among such groups as the Red Cross and the AABB and in pursuit of this goal a non-governmental organization called the American Blood Commission was formed. Representation on the American Blood Commission was intended to be very widespread among interested organizations and in fact the members of the ABC are drawn from all facets of blood banking, from medicine, from hospitals, and from various special interest groups like unions, Blue Cross, hemophilia etc. Needless to say the ABC has been a flop. I suspect that it will hold on to finish a couple of useful projects that it has undertaken but its principal purpose of finding a way to establish a truly national blood policy and philosophy has not been achieved and at the moment I can see no way in which it can be achieved.

Speaking of special interests, we must not ignore the various organizations representing different facets of blood and plasma, each of which has its own axe to grind and in doing so succeeds in making the job in the world that much more complicated. To mention a few, perhaps the most interesting, successful, and unique group is the World Federation of Hemophilia, a loose confederation of national hemophilia societies. This group has been very effective particularly in the U.S. in gaining popular support leading to legislation and authorization of public funds to help defray the cost of the constant care for hemophiliacs. Another group, this one a governmental agency, also is often responsive to pressures of special interest groups. This is the National Heart, Lung and Blood Institute which has a separate division to control the expenditure of public funds for the support of treatment centers, at the moment with special interest in hemophilia and to allocate funds for grants and contract research in all phases of blood banking and fractionation. The American Medical Association is another example of organizations that maintain committees to formulate their own policies and to try to influence the direction of blood and plasma organizations to their own interest. The U.S. Pharmaceutical Manufacturers Association and its international counterpart have sections or working groups devoted to this field of interest. In this context, as some of you know, I have been representing Cutter and the US PMA in a working group on blood and blood products of the IFPMA. This working group has representatives of most of the significant fractionators in the world and its effectiveness has surpassed the expectations of most of us who are members of the working group. Practically all of its interests have been related to problems of European countries, the Council of Europe, the League of Red Cross Societies and the World Health Organization. You will recognize quickly the value of participating, to protect Cutter's ability to market products. U.S. governmental organizations or regulatory matters are simply of collateral concern only as they may affect the thinking or policies

of the multi-national situation in Europe. Also, this IFPMA working group has now succeeded for the first time in bringing together the commercial fractionators and representatives of the International Red Cross Societies. This meeting that was held in Zurich last November was very successful in that it allowed a frank discussion of all of the opposing points of view so that now everyone has a better understanding and will not be so prone to repeat many of the half-truths that have become commonplace in the continuing battle of wits. We plan another meeting this Fall in order to begin pursuing, among other matters, the mechanism by which the relatively scarce technological resources of the world as represented by industry and the Red Cross can be brought to bear over the next decade to assist developing countries to attain some degree of self-sufficiency in blood components and plasma products. I feel very confident that this kind of breakthrough will be of enormous assistance in reducing over the next few years the misunderstandings that often interfere with our own, that is Cutter's marketing efforts.

I mentioned the World Health Organization a moment ago and I thought you might be interested in at least one of the results of my assignment by Cutter to work with the Biologicals Program of the World Health Organization, on projects designed to put together manuals and requirements in blood products to aid in another way the program I just mentioned in the lesser industrialized countries. I mention this because one of the first of these documents has now been published and I want to show it to you but more importantly I thought it would be interesting to you to be aware of the value of this to Cutter.

This publication is the report of the WHO Expert Committee on Biological Standardization, a yearly compilation of the work of the Biologicals Program of the WHO as considered by and, in effect, approved by the Expert Committee. I have been privileged to attend the last two meetings as a consultant and therefore participate in the deliberations.

The significant document in this report is contained in the section running from pages 28-87, over half the book, entitled "Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products". It is noted at the end of the report that a group of 19 people were the authors, of which I was one. I don't mention this, believe me, because I want to toot my own horn, but to point out that all the other authors, with the exception of Barker from Bureau of Biologics, are from Europe - so Cutter is the only U.S. fractionator participating in this important endeavor.

I want to point out why I believe this participation <u>is important</u> to Cutter. I found that by being one of the authors, I was able to prevent the inclusion of requirements for fractions worded in such a way that Cutter products would not be acceptable or would need extensive additional testing. Now what is the value of that? These WHO publications have international authority and influence

greatly the directions of policy and technical standards in countries all over the world, including the U.S. By helping to support the WHO program with a few bucks and my or someone else's time and expenses, we can gain maximum assurance that we have a strong voice in shaping that direction and thus reduce to a minimum the chance that U.S. standards will not be compatible with our products as we would like them to be.

Another, rather one-sided organization, and I say one-sided mainly because of the nature of its members, is the International Society of Blood Transfusion, which, although it has many members from all over the world, is principally a European Organization. Its officers and management have tended to be from the idealist school of blood banking and so have often in their international meetings leaned over backwards in the advocacy of volunteerism, nonprofit and noncommercial blood banking and plasma products production.

So you can see from this short discussion of special interests that just those I have mentioned make a challenging array of actors, each with his own part to play, but sometimes as though there has never been a rehearsal to establish the plot. It doesn't appear as though there will ever be agreement as to what is best.

Fractionation of plasma is of course our principal interest. Commercially it is our only interest. Over the years, the competitive situation domestically and internationally has been changing slowly. Domestically, there have been many dropouts, leaving at the present time the four big ones which I mentioned and there are those now who feel that Hyland is on its last legs, to the point where we feel at ease to speculate as to whether they will be competent to work with the American Red Cross in the construction and efficient operation of their joint venture 1 million liter per year fractionation facility now reputed to be built in North Carolina. In the rest of the world, there are two or three strong multi-national fractionators such as Kabi and Immuno and also odds and ends of nationally dedicated plants in many many countries. Each of these national facilities seems to suffer from its own particular problems of supply of plasma, lack of money, a dearth of competent people and capacity constraints. Looking ahead it is an intriguing task to postulate where all this will go to and how Cutter in its expansion worldwide with the significant urging of our parent company will be able to make a real mark. We can establish plasma collection centers, we can establish filtration, filling and finishing facilities, we can construct fractionation plants, we can expand our market penetration into areas where we are not now represented, utilizing the output from all of these new facilities. We have potential for manufacturing our own plastic equipment to be used in conjunction with this program. In other words, we <u>can</u> do anything. Slowly we have to work out the political and sociological aspects of such aspirations and, believe me, these are not the least of the challenges that we will face. I'll mention again now something that I have been talking about for several years and which I believe to be an important factor in the planning we must do. Besides the U.S. there are only two countries in the world that will allow export of plasma protein collected in that country. These are West Germany and Austria. For all practical purposes, these three countries

(the U.S., West Germany and Austria) are the sources of plasma fractions for every other country in the world, with maybe 2 or 3 exceptions which Lowell and Carroll might even argue with me on. What this means is that the entire developed world except for the United States, West Germany and Austria is not self-sufficient. The impact of this on the U.S., for example, is that somewhere around 20% of plasma protein collected in the U.S. is exported either as plasma or as a product. Now the World Health Organization has established an objective of primary health care for every inhabitant of the world by the year 2000. It may surprise you if I say that 3/4 of the world's population has absolutely no blood service. The few exceptions to this are the rich and the elite. There is no way in which the United States, with the small help of West Germany and Austria, can continue an escalating supply in the face of the pressures that will normally grow out of these programs to establish health care. It's going to be an exponentially rising curve with relatively little increase in the first years, but as health service infrastructure is established in developing countries, that is, better water, better sanitation, clinics, hospitals, and medically trained personnel are acquired, then blood banking and the inevitable spinoffs leading to need for plasma processing will become quickly apparent. With a very large number of these countries located in areas with significant disease vectors leading to high levels of hepatitis, malaria, parasites and so forth, blood and plasma for the needs of those countries will have to come from those countries themselves. I could not imagine plasma from a country with 50% hepatitis B positive donors being shipped for fractionation to any of the plants located in the developing countries. The question is what will our role be in finding answers to these dilemmas? It is something to think about.

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