

Positioning a Blood Center to Grasp Biotech Opportunities

By EDWARD P. SCOTT, M.D.

The modern age of blood transfusion began after the Second World War, as detailed in Douglas Starr's book, *Blood: An Epic History of Medicine and Commerce*.¹ During the war, it became apparent that early and aggressive medical treatment utilizing whole blood or plasma could increase the chances of survival for military personnel wounded in combat. In the United States, a national program to encourage blood donation was created to provide the needed blood, which was then shipped as whole blood or plasma to war zones. After the war, physicians were eager to apply surgical advances developed on and off the battlefield to the care of the general population. Because these advances relied on blood transfusion, for the public to realize their benefit, adequate supplies of whole blood and blood components needed to be available to hospitals across the country. This was often not the case.

The national effort to promote blood donation during the war was largely dismantled as the war ended. Many local communities lacked a coordinated program to recruit blood donors and to collect and prepare donated blood. In some large cities, blood programs that had been managed by the American Red Cross, the local medical society, or another agency during the war were reactivated or refocused to provide

blood to community hospitals. In other cities, each hospital took responsibility for its own blood supply and managed its own donors, who were usually family members or friends of patients who needed blood. Because these latter programs operated under the precept of "individual responsibility," a patient's medical care was often postponed until an adequate supply of blood had been donated. Both the community-wide and hospital-based programs had to rely on professional "donors" who were paid for providing blood to supplement the usually insufficient supply provided by volunteers.

The Memphis Experience and the Stimuli for Change

1963–1972

Prior to 1963, "individual responsibility" programs provided blood for patients in Memphis. Each hospital collected blood for the sole use of its patients. For years, chronic supply problems had prompted local physicians to attempt to create a community-wide blood program that could increase the community's overall supply and reduce supply inequities among hospitals. In 1963, the not-for-profit Community Blood Plan of Memphis (CBPM) was created under the auspices of the local medical society and the hospital association. However, in its early years, the CBPM promoted blood donation to individuals and organizations throughout the community but performed no blood collection, testing,

storage, or distribution. It was a "dry" blood bank.

1973–1982

After a decade, it was apparent that additional efforts were needed to increase the availability of blood in the Memphis area. The hospital-based collection programs were unable to meet the needs of all patients, and blood from paid donors, which had been shown to have a high risk of transmitting hepatitis, was being used regularly for transfusion. In 1974, the CBPM began recruiting donors to a donor center that collected blood for the entire community's benefit, not just for a single hospital. The Plan continued to assume additional responsibilities for the blood needs of Memphis and the growing surrounding area. To reflect that growth and its expanded reach, the organization's name was changed to the Mid-South Regional Blood Center and the business name of Lifeblood was added.

1983–1992

This decade began the transformation of Lifeblood and all other blood centers from "blood banks" into current Good Manufacturing Practices (cGMP)-compliant biologics manufacturing operations. This transformation was guided by FDA's increasingly restrictive regulations and recommendations regarding blood and blood products. Because of concerns about transfusion-transmitted infections — especially HIV — blood centers became (and continue to be) bellwethers for regulation of bio-

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logical materials in the United States. Significant costs were incurred as measures were implemented to comply with these regulations. Because blood centers have narrow product lines and a relatively small number of customers, these costs had to be passed on to the hospitals that transfused the blood products. As a direct consequence, the average price for red blood cells (the primary component used for transfusion) in the United States increased by more than 50 percent during the decade (Fig. 1).

1993–2002

Lifblood and other blood centers continued their move toward cGMP compliance under the guidance of FDA by strengthening infrastructure, adding overhead in the form of staff to assume additional review and oversight responsibilities, and making myriad additional process improvements. These efforts were all associated with additional costs, again causing the average red blood cell price to double within a decade (Fig. 1).

During this period, the Lifblood

blood center generated more than 95 percent of its revenue from the sale of transfusable blood components to local healthcare facilities. As costs increased and customer resistance to accepting them as “pass-throughs” grew, it became necessary for Lifblood to seek other revenue opportunities to cover expenses and build reserves. In 1999 a new department, Lifblood Biological Services (LBS), was created to focus on products and services that could potentially be provided to an alternate group of customers and generate excess revenue to support the core business of providing blood for transfusion. Non-core activities (i.e., those not directly associated with collecting, preparing, storing, or distributing a transfusable blood component to a local customer) became the responsibility of LBS. This allowed LBS staff to focus on identifying and meeting the product and service needs of non-core customers and allowed core staff to focus on providing services to the organization’s traditional customers.

Lifblood Today

As it enters its fifth decade of operation, the organization’s core business remains the provision of transfusable blood components and related services to healthcare facilities in the Mid-South. The core competency that allows this to occur is the ability to source, process, store, and distribute human-derived biological materials (HDBMs) in an efficient, cost-effective, and cGMP-compliant manner. Opportunities for blood centers to support cell and tissue bioprocessing have been readily available, but often have not been grasped due to real and perceived barriers.² For the Lifblood blood center, a first step toward overcoming these barriers was to recognize the organization’s core competency and elucidate the opportunities that could follow if that competency was applied in new ways.

Lifblood assessed its current operations for existing but unpursued opportunities related to production and supply of HDBMs and determined that it already handled more than 250,000

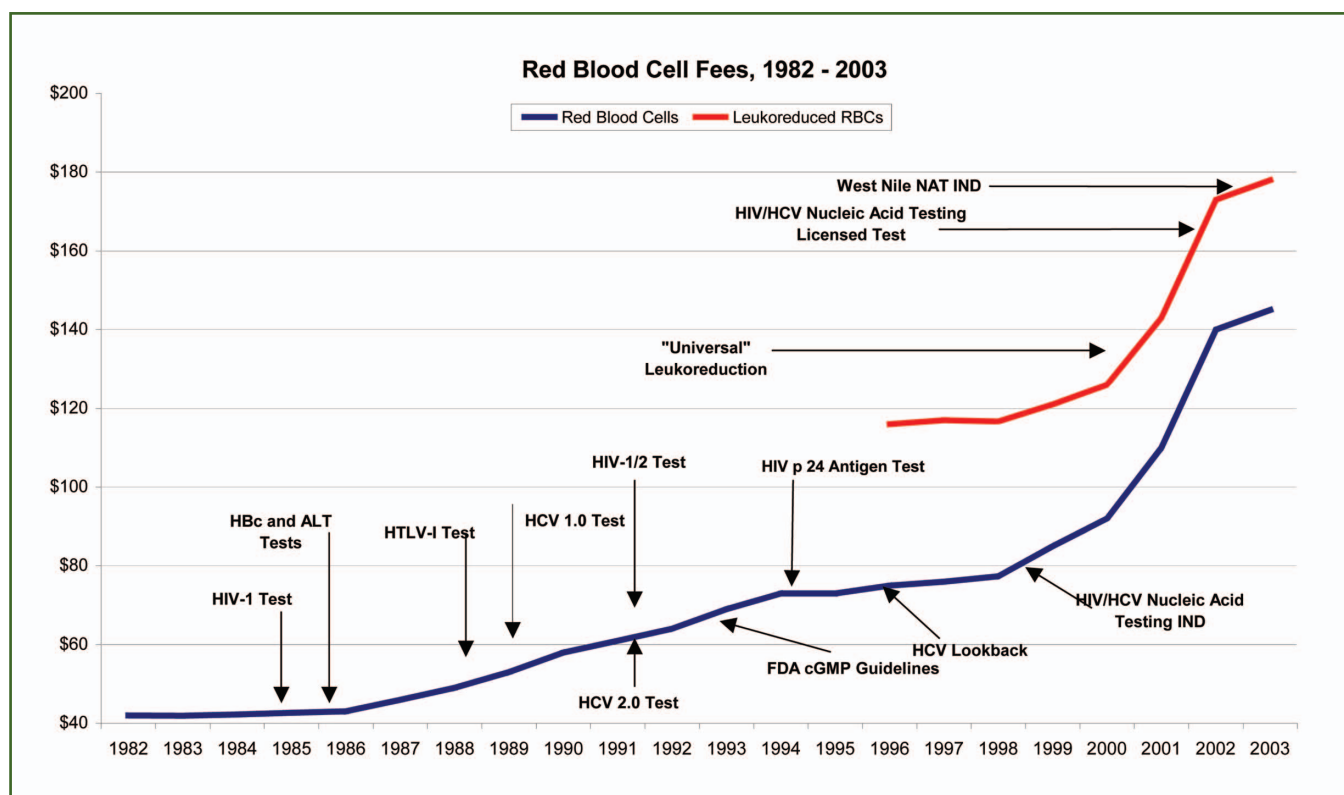


Figure 1. Increase in the average fee charged by independent regional blood centers in the United States for provision of red blood cells for transfusion from 1982 to 2003 associated with the implementation of safety measures to reduce the risk of transfusion-transmitted infections. Source: America's Blood Center

products annually that could be defined as such. The list ranged from discarded blood sample tubes to red blood cells for transfusion. Only about half were blood components provided for direct patient transfusion. Approximately one quarter were sold for further processing into injectable products for patient care (e.g., intravenous immune globulin and albumin). The remaining fraction had the potential to be sold for support of research or product development, or discarded if no biological use could be identified. Lifeblood Biological Services began operations by focusing on this fraction and has grown and matured as the staff has increased its knowledge of the products and services that can be provided to a new group of customers.

Growing a Business Within a Business

Stage 1 (supplier)

Prior to the creation of LBS with its dedicated staff, the Lifeblood blood center had received requests for provision of non-transfusible HDBMs, but could not effectively respond due to a lack of appropriate infrastructure. To address these missed opportunities but control costs while doing so, LBS initially had only one staff member. Her duties consisted of locating “secondary” customers for blood components that could not be used for transfusion by the center’s primary customers. These products were not transfused because they were either unacceptable, due to a production or storage failure or reactive infectious disease test results, or because they were unneeded during their limited shelf lives.

The latter group consisted primarily of platelet components (whole blood or apheresis-derived) that remained untransfused during their five-day shelf life. Smaller numbers of outdated red blood cells (primarily type AB or type A, which are available in quantities exceeding transfusion needs) were also sold. Production and storage failures included preparation or storage of components outside of cGMP-defined time and temperature parameters. A key revision of the infrastructure that allowed LBS to take advantage of this market opportunity was the creation of

a data management system that assured consistent tracing and tracking of these products, which historically had been destroyed to prevent release for transfusion.

During this first stage of growth, relatively little additional revenue was generated (approximately \$75,000 in the first year of operation), which was coupled with an undefined amount of cost reduction due to avoiding disposal of unacceptable components. However, the greatest value gained from this stage was the staff member’s expanding knowledge of the secondary markets for these and other products, as well as the relationships being built with potential buyers.

Stage 2 (value-added supplier)

As relationships were established with customers for these products, the staff learned that within a broad class of products, such as outdated blood components, were higher value subcategories. The premium value may relate to the presence of easily defined donor characteristics, such as sex or race, or may depend on the presence of other information, such as human leukocyte antigen (HLA) phenotype, that is not routinely available but which can be determined. As staff learned how customers perceived the value of these products, efforts were made to add the more highly valued subcategories to the product line.

To avoid incurring additional costs that would have to be borne by core customers, barter arrangements were often used to establish these new product lines. In order to create or increase the availability of raw material, a customer may be willing to help LBS create or expand capabilities to supply the product. An example of such customer-supplied service is performance of HLA- or platelet-specific antigen typing of a group of donors to identify those that could provide products with the desired phenotypic expression of the antigens. As compensation for such a service, LBS may provide a portion of the needed products to that customer at reduced cost.

In this example, core customers and the community would also benefit from

a resource, a cadre of HLA- or platelet antigen-typed donors, without having to bear the associated “creation” costs. This new community resource would allow effective support of patients with preformed HLA- or platelet-specific antibodies who could not be supported otherwise. A win-win-win situation results — the “alternative” customer gets access to a critical raw material for product manufacturing, core customers get a resource for the community at no upfront cost, and Lifeblood adds two value-added product lines: an alternative product line that generates revenue through LBS, and a core product line, phenotyped platelet products, that generates revenue from core customers.

During this stage, needs for blood components that are fully acceptable for transfusion, but that have a higher value if diverted for alternative uses, began to be identified. This opportunity created a need to develop processes and systems to prioritize product usage, which prompted a reassessment of the value of blood components to individual customers and the value of those customers to the organization. For example, Lifeblood is aggressively expanding recruitment of African-American whole blood donors to increase red blood cell availability for patients with sickle cell anemia who are receiving chronic transfusion therapy for prevention of stroke. “Themed” blood drives in the African-American community have resulted in relatively large numbers of whole blood units collected at a single event. Traditionally, platelet concentrates, which only have a five-day shelf life, would not be produced from these whole blood collections if the blood center’s platelet supply was adequate. In that case, only red blood cells and plasma components would be produced, basically wasting the platelets.

However, a secondary market for African-American platelets exists among diagnostic test manufacturers. Therefore, there is value in producing as many platelet concentrates as possible from these donors so that they can be supplied to the test manufacturers (and not wasted.) This broader market view generates revenue that would be missed with a traditional market focus. As

opportunities such as this developed, it was essential that effective internal and external communications were in place within the organization to ensure that the needs of all customers were being addressed and all opportunities to provide service and generate revenue were being evaluated.

During this stage, the staff progressed from selling outdated components to sales of “pre-outdated” products (i.e., products that are expected to eventually outdate due to lack of need for transfusion therapy, but which have a higher value or additional uses if sold while in-date). Opportunities to generate products not currently provided by the blood center were also identified and pursued (e.g., pooled human serum, AB plasma, or AB serum from non-transfused male donors). This opened up a new group of customers and the growth cycle continued. Revenue during this period averaged approximately \$100,000 per year.

Stage 3 (contracted collections, services, and consultation)

In response to requests from customers, LBS expanded its line of products to include apheresis-derived mononuclear cells (MNCs) that were used to support clinical studies of autologous dendritic cell vaccines. Building on this experience, the ability to supply MNCs for use in preclinical research and product development was quickly added. These MNC products were primarily used to develop or refine manufacturing processes for biotherapeutics being assessed as potential therapies for malignant or immune-mediated conditions. Each customer had a unique intended use for the cells and as staff gained an understanding of a customer’s unique needs, they developed the capability and expertise to recruit donors and collect products to that customer’s specifications. This included recruiting donors to match specific selection criteria (e.g., age, sex, race, HLA type, and health and/or medication history) and collecting products in accordance with specific requirements (e.g., AutoPBSC™ or “manual” MNC collection protocols, blood volumes processed, target product volume, and collection of ancillary

products such as plasma and/or whole blood from donors). These “collections to specifications” have become a market niche for LBS.

For customers developing autologous cellular therapeutics, MNCs from these specialized collections provide an opportunity to perform preclinical analysis of manufacturing processes with raw material that closely mimics that which will be used in clinical studies. This allows more effective and efficient proof of concept, which in turn may enhance early-stage funding support for the customer. For example, access to products collected from donors with a specific cancer has enabled manufacturers to evaluate the ability of their products or processes to impact a targeted cell subset collected from an environment that mimics the proposed patient population. Without this option, the customer may not have an opportunity to evaluate the effect on cells from the targeted population until Phase I trials are underway.

As staff worked with customers who used MNCs as raw material for development of biologics, it became clear that the customers had limited experience and expertise with blood component collection. This is not unexpected; however, to assure consistent development of the biologic, standardization of raw material collection could be critically important. By varying collection parameters according to customers’ specifications and providing collected products to them for evaluation, LBS staff provided customers with opportunities to define optimal protocols for cell selection that met their manufacturing needs. Because of their experience with storage and shipment of biologics, LBS staff have also been able to assist customers in developing their unique approach to cGMP issues for their products.

In a year and a half, demand for MNC products grew from one or two products a month to nearly forty a month. To supply the needs of this rapidly expanding customer base, collection capability was increased several fold by acquiring additional COBE® Spectra™ apheresis machines and adding staff dedicated to the collection of these and other products for LBS

customers. These capacity enhancements were for the exclusive support of non-core customers. To date, growth in this product line has been due to word of mouth “advertising” by customers and rudimentary marketing efforts by LBS staff. This growth was primarily responsible for LBS’ annual revenue tripling (compared to Stage 2).

Current stage (supply, services, and manufacturing)

In response to requests from customers, LBS has created capacity to produce “research ready”SM components, allowing a researcher to focus on those activities that are the highest value to the institution (i.e., those associated with the performance of actual research, rather than preparation of reagents). This is possible because we have installed equipment that allows staff to perform preparation steps commonly used to prepare raw materials for research. For example, immunomagnetic selection of cell subsets from MNC products can be accomplished using a CliniMACS® system (Miltenyi Biotec, Cologne, Germany).

To expand our ability to provide research-ready products, we added staff to focus on development and marketing, and added additional equipment to provide more functionality. For example, through an arrangement with a manufacturer, we acquired a pre-market version of a counter-flow elutriation device to assess both its capabilities and the feasibility of using the device to produce cell fractions for research support. This benefits the equipment manufacturer, Lifeblood, and researchers.

For the manufacturer, this provides an opportunity for placement of cells processed on the device into researchers’ labs prior to equipment licensure, thereby demonstrating the quality and value of the products that can be produced using the equipment. For the researchers, it allows an early assessment of the quality of the produced products before committing to purchase the equipment — a cost-effective “try before you buy” approach. For LBS, it allows creation of additional product and service lines.

By sourcing, collecting, and processing raw material into research-ready

products to meet customers' specifications, LBS provides economies of scale benefits to biotech customers that are similar to those enjoyed by Lifeblood's traditional blood component customers. This centralized approach allows equipment and raw material use to be optimized and allows researchers to have access to raw material that optimizes the use of limited research dollars and facilitates product development. In the future, other cell processing capacity for generation of cell subsets and *ex vivo* expansion of cells will be added, enabling LBS to expand its line of research-ready products.

Looking Forward

To date, LBS has not produced "mobilized" MNC products collected from donors pretreated with granulocyte colony-stimulating factor (G-CSF); however, these products will be added to allow them to be supplied as raw mate-

rial to researchers and to allow their use as raw material for in-house production of additional value-added materials for research support. Additionally, products from other human cell sources, such as bone marrow and umbilical cord blood will be included in the product line. Lifeblood Biological Services plans to continue to gain knowledge and experience in these new areas of cell processing with the ultimate goal of creating the capacity to perform contract manufacturing of cellular therapeutics in a pharmaceutical-grade cGMP-compliant facility.

In the next five years, LBS will build on the experience gained to date and will continue to seek opportunities to expand its range of products and services. Two keys for success will be aggressive pursuit of opportunities for growth and maintenance of an infrastructure that is poised to take advantage of opportunities as they are identified.

In the current fiscal year, LBS' reve-

nue and expenses represent less than 5% of the respective totals for the Lifeblood blood center; however, net revenue generated by LBS activities represents 29% of the organization's total. It is important that more options to generate revenue from sales of non-traditional components be found in order to further protect core customers from having to bear rising costs associated with the core business. Continued diversification of the revenue stream through LBS' growth will strengthen Lifeblood and help assure that it continues to fulfill its community service mission, serves its customers well, and achieves its strategic goals.

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