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# Cell and Tissue Bioprocessing: Opportunities for Regional Blood Centers

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Within the United States, greater than 90% of the available transfusible blood products are collected, processed, and distributed by regional blood centers. The remaining blood products are collected by hospital-based blood banks and are usually provided only to patients in the collecting facility. The "region" in which a blood center offers services (i.e., collecting blood from volunteer donors and providing blood components to healthcare facilities), is usually an arbitrarily and independently defined group of contiguous counties surrounding a major metropolitan area. However, the borders of the region can be elastic and easily altered by gaining or losing access to donor groups or customers. It is not uncommon for a geographic area to be simultaneously "claimed" by neighboring competing blood centers.

America's Blood Centers (ABC) is a not-for-profit trade organization that provides services and advocacy for independent not-for-profit regional blood centers. ABC's seventy-five members collect approximately 45% of the country's blood products. Each center operates under a unique license issued by FDA. Professional staff under the guidance of volunteer leadership manage each center. The American Red Cross (ARC), also a not-for-profit corporation, collects and distributes a similar amount of blood products through a network of thirty-six regional centers which operate under a single FDA license. Professional staff in ARC's regional centers are under the direction of managerial staff at its national headquarters. A volunteer board of directors in turn guides these managers.

The core functions performed by blood centers have remained basically the same for decades. These include: recruiting and qualifying individuals to serve as volunteer blood donors, collecting whole blood or blood components from donors, processing the whole blood or components into transfusible products, maintaining those products in a controlled environment until needed, and distributing the products to healthcare facilities. The principal components used for transfusion in the United States are, in decreasing order, red blood cells, platelet components, and plasma components (fresh frozen plasma and cryoprecipitated antihemophilic factor.) These products can all be produced from whole blood using minimally complex manufacturing steps, including separation of the component elements by their relative specific gravities using differential centrifugation, or by their freeze/thaw characteristics.

Although blood centers' core functions have remained basically unchanged, the processes used to perform these functions have become more complex. Increasingly, whole blood collections are being supplemented by specific blood components generated using closed system separation (apheresis) technology that removes only selected blood components. This allows a higher concentration of the desired component to be obtained from a donor than would be possible with whole blood collection. Transfusible products routinely collected by apheresis include platelets, red cells, plasma, and granulocytes.

Laboratory screening of blood components has also increased in complexity with the addition of multiple tests to detect potentially infectious components. Currently ten tests are performed on all donated units whereas only two were available twenty years ago. Included in the current tests are three that employ nucleic acid technology to detect viral RNA.

Finally, to protect at-risk patients from other post-transfusion complications, an increasingly large fraction of blood components is now subjected to additional processing steps prior to transfusion (e.g., depletion of contaminating leukocytes by filtration or exposure to gamma irradiation to "neuter" T lymphocytes that may cause graft-versus-host disease.)

## Transformation of Blood Centers

After it became evident in the early 1980s that human immunodeficiency virus (HIV) could be present in the blood of an asymptomatic blood donor

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| Table 1: Opportunities for Support |
| --- |
| Production / Supply of Raw Materials |
| Contract Manufacturing |
| Inventory/Distribution |
| Consultation / Education |

and subsequently transmitted by transfusion to a recipient, the public became understandably concerned about the safety of blood transfusion in the United States. During the last two decades, this concern has expanded into a public expectation that transfusion of blood could — and should — be made *risk free.* This expectation has been uncoupled from any concern for the cost-effectiveness of measures that would be used to achieve it. To a large degree, the U.S. Congress shares the public's view and has placed increased pressure on FDA to implement and enforce regulations that would achieve this goal in as short a period as possible.

This regulatory pressure, coupled with public expectations and a wave of litigation, transformed blood centers from relatively unsophisticated and autonomous community service organizations into highly regulated cGMP-compliant biological product manufacturing companies that must adhere to national performance expectations. Blood centers became and continue to be bellwethers for regulation of biological materials in the United States. FDA has used the requirements for blood donor screening criteria, infectious disease testing, and blood component processing as models for regulations that have been, or ultimately will be, applied to the sourcing, processing, storage, and distribution of other biologics (such as tissue, hematopoietic progenitor cells, and mesenchymal cells.)

Substantial infrastructure within blood centers has been added at great cost to meet the stream of additional regulatory requirements placed on transfusible blood products over the last two decades. This has included adding numerous staff that must perform an increasing number of non-revenue generating functions such as training, counseling deferred blood donors, managing product recalls and withdrawals, information management, and quality assurance. Significant costs were also incurred to introduce enhanced blood donor and blood product screening to reduce transfusion-transmitted infections. Advances in transfusion therapy have significantly increased the safety of blood for transfusion but have also increased the cost of medical care in the United States by nearly $2.5 billion per year compared to twenty years ago.

Each blood center serves a relatively small number of hospitals and other healthcare facilities and provides a narrow line of products, most of which are in the mature or declining stage of their product life cycle. Nearly all of a center's revenue is generated from the sale of transfusible blood products. This combination of a small customer base and limited product line has made it necessary for blood centers to attempt to pass most compliance-associated costs incurred over the last fifteen to twenty years to their primary customers through price increases on blood products. However, during this same period, healthcare facilities have experienced declining reimbursements from third party payers and have resisted accepting increased costs from any service vendor, including blood centers. This creates significant tension as blood centers attempt to recover their costs and their customers simultaneously attempt to reduce expenses. Unless other options can be identified, this adversarial relationship can be expected to continue and worsen because the cost of providing blood for transfusion may double in the next few years due to the expected introduction of pathogen inactivation of cellular blood products.

Blood centers' core business will, for the foreseeable future, continue to be the provision of transfusible blood components and related services to healthcare facilities. However, the core competency that allows this to occur is the ability to source, process, store, and distribute human-derived biological materials in an efficient, cost-effective, and compliant manner. This, along with a blood center's established infrastructure, is a valuable resource that can be applied to the management of other biological materials. These materials could be marketed to non-traditional customers to provide net revenue to offset or absorb some of the escalating costs associated with core services, in turn offering some fiscal protection to a blood center's primary customers. Biotech companies that use human-derived biological materials in research and product development are ideal customers for these products and associated services. If successful, expanding a product line and customer base in this manner creates a win-win-win arrangement in which a blood center's core customers receive some degree of cost protection, new customers receive needed products to support their growth, and the blood center is positioned into a expanding market with products that are in the growth stage of their product life cycle. Blood centers currently have the experience, infrastructure, relationships, and expertise to assist and support biotech companies (Table 1).

## Production and Supply of Raw Materials

Because many biotech companies rely on raw materials (blood cells) that must be sourced from recruited, qualified, and informed and consented human donors, this is an area of immediate opportunity and a perfect fit for a blood center. In fact, many biotech companies currently rely on blood centers for biological materials used for research and product development. These include standard whole blood and apheresis-derived blood products, standard and non-traditional blood products collected from donors specifically selected to fulfill a biotech customer's unique requirements, and

"byproducts" of routine blood banking that are not or cannot be sold for transfusion. Typical examples of biotech applications for whole blood and apheresis-derived biological materials are shown in Table 2.

Blood center sourced red blood cells are used in analytical systems either as target reagents or as controls. They are also used to immunize plasma donors and boost levels of a targeted antibody (Rh immune globulin, for instance). Outdated, and some in-date, red blood cells are used in development of human hemoglobin-based oxygen-carrying compounds that may be useful as red cell substitutes for transfusion. Platelets are used as targets or controls in analytical systems in the same manner as red cells. Plasma produced as a byproduct of red blood cell production from whole blood is manufactured into injectable therapeutics, such as albumin and immunoglobulins, or non-injectable products. Serum from sample tubes obtained with each whole blood collection is pooled and used to prepare diagnostic controls.

Mononuclear cells collected from whole blood products or by apheresis are increasingly being used to support biotech research and product development. Leukocytes, removed from red blood cell products prior to transfusion to reduce the risk of transfusion reactions, are used as raw material for the production of human interferon. Whole blood samples containing nucleated blood cells, along with extended and detailed health histories, are obtained from blood donors for use as "normal" controls in DNA repositories. Increasingly, mononuclear cell products are used to produce lymphocyte fractions to support research into the mechanisms of immune modulation. Dendritic cells prepared from autologous mononuclear cell concentrates are being used to develop cellular vaccines. Finally, adult progenitor cells collected by blood centers using apheresis are supplied both for direct clinical applications and for associated research.

**Table 2: Blood Center Sourced Biotech Biologics**

| Blood Product | Application |
|---|---|
| Red Blood Cells | Reagent Red Cells |
| | Control Cells |
| | Immunizing Cells |
| | Hemoglobin Source |
| Platelets | Reagent Cells |
| | Control Cells |
| Plasma | Injectable Therapeutics |
| Serum | Diagnostics Control Sera |
| Mononuclear Cells | Interferon Production |
| | Genetic Material Repositories |
| | Lymphocyte Fractions |
| | Dendritic Cells |
| | Progenitor Cells |

**Table 3: Blood Center Sourcing Environment**

| | |
|---|---|
| Standard operating procedures | √ |
| Qualified donors | √ |
| Informed & consented donors | √ |
| Compliant collections | √ |
| Compliant product handling | √ |
| Traceability and trackability | √ |

## Production and Supply Opportunities

In addition to a potential price advantage (compared to sourcing through brokers), blood centers' regulated processes offer other benefits to biotech customers (Table 3). As the original source of the product, the donor selection, product collection, storage, and shipment are all under a blood center's control and are carried out in the cGMP environment created for transfusible blood components. Raw material sourcing needs for biotech companies are very similar to the standard practices that blood centers employ to collect their products. Therefore, fitting these special collections into a blood center's operations should not be difficult and, consequently, biotech companies should have to look no further than to blood centers to find companies that have the infrastructure and capabilities to collect the human blood-based raw materials they need.

Biotech companies will also require human-derived biological materials that have even less in common with traditional blood components than those described above. These include umbilical cord-derived products, bonemarrow-derived mesenchymal cells, adipocytes, and peripheral blood-derived cells that have no identified transfusion value. To provide these materials, blood centers will have to create the capability for their sourcing, processing, storage, and distribution.

**Table 4: Product Manufacturing Environments**

| | Blood Centers | Biotech |
|---|---|---|
| Staffing qualifications | MT/OJT | MT/OJT |
| Documentation of staff training | √ | √ |
| Strict adherence to approved procedures | √ | √ |
| Contemporaneous documentation of work performed | √ | √ |
| Control of raw materials | √ | √ |
| Control of manufacturing reagents | √ | √ |
| Validated equipment | √ | √ |
| Strict traceability and trackability | √ | √ |
| Quality Assurance/Quality Control | √ | √ |
| Manipulation level | Minimal | Complex |
| Environmental needs | "Tidy" | Clean |
| Compliance level | Biological | Pharmaceutical |

Only a few may choose to do so because even current opportunities to create customer-supplier relationships between blood centers and biotech companies for products that are closely akin to blood components are often not being realized. Barriers to these relationships lie primarily within the blood centers and include the following:

1) The core business of the blood center is the collection, processing, and distribution of blood components for transfusion. Fitting specialized collections for non-core customers into core activities is often seen as an inconvenience instead of an opportunity. Each apheresis procedure can require three to four hours of donor and staff time, thus making the staff and equipment unavailable for standard blood component collection. Although blood centers would most likely agree to collect these products for biotech companies if requested to do so, such products are given secondary priority and equipment and personnel will be redirected to standard collections if needed. This could make a blood center a less reliable provider for these products, causing the customer to seek more consistent sources.

2) A degree of preparation is required before these specialized collections can be implemented. For example, procedures have to be written *de novo* or existing procedures have to be modified and approved by internal compliance authorities. Staff have to be trained, which may include minor or major variances from standard procedures (e.g., donor selection criteria, product labeling requirements, and product storage and shipping requirements.) Costs associated with this training are in addition to the cost of the product collection and must be determined and recovered. Blood center staff may be unwilling or unable to perform this degree of cost accounting, especially when the procedures are infrequent and limited in number. Consequently, blood center management can be hesitant to support such programs without assurances that they will generate net revenue.

3) If individuals who incidentally or expressly do not meet standard donation acceptance criteria are recruited as donors, they must be recruited and managed differently than routine donors. Blood center personnel often have no experience in this area and would have to develop that skill, which may result in initial inefficiency of effort and added costs. Additionally, staff may be unwilling or unmotivated to develop these skills if they do not appreciate the value of the non-traditional collections for the blood center.

4) Donors of these products are usually compensated. Even if the customer, not the blood center, provides this compensation, it may cause concern for staff and could cause conflict among a facility's volunteer donors. Also, mechanisms for handling compensation have to be developed and may require collection staff to dispense cash. Obvious concerns arise over the ability to manage and trace these funds.

5) These biologic products often must be managed in a manner that differs from standard products, and staff expertise must be gained in that process. For example, these products are unlikely to be licensed by FDA and will not have a standard blood product code assigned. Therefore a blood center's computer system may not allow facile tracing and tracking as it would for routine components. This may require creation of "workarounds" or manual record systems for managing these products. Such deviations from standard controls create the potential for errors; thereby creating an element of risk a blood center may be unwilling to accept.

6) As a not-for-profit corporation, a blood center's mission of service to its community should guide its operations. The definition of the center's *mission* and *community*, as stated in its charter, and the degree of restriction placed on the operations by the governing volunteer board may prevent pursuit of these "non-traditional" products and services.

7) Most of these collections are strictly to support research and, therefore, their collection would fall under the purview of a Human Subjects Review Board. A blood center may not have, and may be unwilling to pursue,

access to such a group. Completing and submitting projects for review has become more complex, time-consuming, and costly over the last several years as has the required documentation and reporting of a study's progress. The blood center staff may not have the expertise to perform these tasks and, if not, will have to acquire it at some cost.

### Contract Manufacturing Opportunities

Similar to raw material supply requirements, many biotech companies' production needs closely align with blood center capabilities (Table 4). Similar minimal staffing qualifications are used in biotech companies and blood centers with reliance on in-house training programs to prepare personnel lacking technical experience to perform required tasks in a cGMP-compliant environment. Although details such as the reagents and operating environments may vary, both biopharmaceuticals and blood products must be produced in an environment that includes the following elements: documenting staff training before performing tasks, creating and adhering to standard operating procedures, contemporaneous documentation of work performed in compliance with procedures (preferably through computer-based data management systems), qualification of raw materials and processing reagents prior to their controlled release, validating equipment before use, strict traceability and trackability of materials and products, and active oversight by independent Quality Assurance staff.

Although the complexity of blood component processing has increased over the last two decades, it does not, at the present time, rise to the level of "more than minimal manipulation." Biopharmaceutical manufacturing of biotech products requires a higher level of manipulation — and more stringent environmental requirements — than for standard blood products. For example, although temperature controls must be in place for production and storage of blood components, there are no established requirements for air quality. To produce pharmaceutical-grade biologics, blood centers may have to implement significant infrastructure enhancements that include cleanrooms. Because of high construction costs, it is unlikely that blood centers will take this initiative "on spec" (i.e., without committed revenue sources to justify the expense.) The lack of qualified space has limited opportunities for blood centers to enter this line of business and has also limited the options that biotech companies have for suppliers of these services. These barriers were overcome, in at least one instance, by a biotech company that funded a cleanroom within a blood center to provide a manufacturing facility for the company's use.

### Inventory and Distribution Opportunities

Blood centers inventory and distribute more than forty million biological products produced from more than fifteen million individual lots each year. They have established processes and procedures to comply with FDA requirements for blood components, which in turn should meet the requirements of biotech customers. These products have shelf lives that range from less than twenty-four hours to many years and must be maintained in continuously monitored, controlled storage environments that have remote alarm notification. Blood centers have experience assuring that distribution of a product occurs in a manner that assures its integrity. Products are transported only in shipping containers validated for the extremes of temperature range and transport conditions expected for each specific product. Traceability and trackability are maintained using bar code labeling and robust information management systems that allow rapid location of products. Contemporaneous documentation of product storage, shipment, and transport assures that chain-of-custody is maintained.

Extremely low temperature (i.e., vapor phase of liquid nitrogen) storage is not standard in blood centers; however, many centers have created the capacity to source, store, and distribute human umbilical cord blood samples that do require these conditions. Therefore, other biologic products with similar storage requirements could be added, albeit in separate and isolated equipment.

Blood centers must maintain the capability to supply healthcare facilities in their region with just-in-time delivery of biological materials. These same facilities will be customers for biotech products, some of which will have similar availability requirements. However, because of the cost and storage requirements of these products, healthcare facilities are likely to be hesitant or unable to maintain a reserve inventory. To assure supply, it may become necessary to create regional cGMP-compliant storage and distribution facilities for these products. Blood centers could easily and efficiently fill that need, eliminating the cost of facilities constructed specifically for this purpose.

### Consultation and Education Opportunities

Biotech companies may have some experience with managing the administration of these products to patients. However, in practice, biologic product administration shares many characteristics of a blood transfusion, including the same level of product control. Blood centers (and hospital blood banks) are clearly the experts in administering biologics to patients and assuring that product control, patient identification, documentation, and patient follow-up measures are in place before the product is administered. As such, they are a ready source of information on the application of these processes to other biologics. Biotech companies often develop from research laboratories in academic medical centers. Therefore, the principals may have some experience in handling research-grade products in a setting in which they supply products directly to clinicians who administer them without having to deal with the traditional hospital "infrastructure."

However, if they become licensed products they may be distributed by regional blood centers to hospital blood banks, and then provided to patients. It could be to a biotech company's advantage to seek guidance from the blood center on issues that affect acceptance of the product, such as packaging, shipping and storage constraints, shelf life limits, and key decision makers.

## Conclusion

The financial and regulatory environments in which blood centers operate are challenging, but within these challenges are also opportunities. The biotech-related opportunities are very real; however, unfortunately, few are being embraced by blood centers due to perceived or real barriers.

To succeed, provision of non-traditional biological products must recover all associated costs and generate excess revenue that reduces the financial pressure of a blood center's core customers. Due to constrained reserves, blood center management may be unwilling to put "venture" capital toward developing these new programs. To circumvent this barrier, it may be possible to raise philanthropic funds for support of these programs, which, if successful, will strengthen the blood center and its relationship with its primary customers.

In addition to the lack of revenue referenced above, there is a lack of staff expertise regarding creating these new products and services. This includes a lack of knowledge of and access to the decision makers in biotech with whom partnering relationships could be developed. To overcome these barriers, it will be necessary for the blood center to actively cultivate these relationships. This can be done relatively easily through membership in local, regional, and national biotech associations that provide opportunities for education and relationship building.

Historically, blood center leaders have downplayed the risk of maintaining the status quo and have generally taken a passive approach to opportunities that lie outside the boundaries of their core business. But it would be shortsighted to ignore the opportunities that exist for blood centers in cell and tissue bioprocessing. All of the barriers listed above can be overcome with the commitment of a blood center's senior leader who sees the value of seizing these opportunities and assures that measures are in place to accomplish the core business while the framework for the future is being laid. By doing so, blood centers will be positioned for a key role in the next wave of transfusion medicine, which will certainly include biotech products based on human-derived biological materials.