

## **Executive Summary**

### **Delivery of Artificial Blood to the Military**

The Committees on Armed Services of the 102nd Congress directed the Secretary of the Navy, on behalf of the Department of Defense, to report on current technology and prospects for development of a safe, effective, commercially produced blood substitute approved for clinical use. Recommendations to accelerate availability of such a substitute to the military and the Nation were also sought. The Assistant Secretary of the Navy (Research, Development and Acquisition) directed the Chairman of the Naval Research Advisory Committee (NRAC) to convene a panel to address these issues.

The House of Representatives Conferees Report directed the Department of Defense to provide an assessment of all "promising emerging technologies and ... assess each technology's potential to satisfy civilian artificial blood supply needs...." The tasking specified that this assessment be fully coordinated with the National Institutes of Health and "any other public or private sector activity involved in artificial blood substitute development.

The NRAC Panel was specifically designed to comply with the Congressional guidance and included representation from relevant technology areas of industry, academia and government. The Panel Membership consisted of internationally recognized experts in their fields from the National Institutes of Health, the Food and Drug Administration, the Office of the Secretary of Defense, colleges and universities, and industry. This group included active and retired officers from the Medical Corps and Medical Service Corps of the U.S. Navy, U.S. Army, and U.S. Public Health Service.

The Panel met over a five month period (March - July 1992). Because of the intensely competitive nature of this industrial field, all meetings were held in closed session. Panel members were screened for conflicts of interest, approved by the Office of the Secretary of Defense, and appointed as Special Government Employees (SGE) if not already full-time government employees. All Panel members signed "non-disclosure agreements" before access was provided to any proprietary information. Because of the importance of this project, the Navy obtained authorization from the Food and Drug Administration (FDA) for Panel members from the FDA to discuss in closed-session "FDA information regarding artificial blood otherwise exempt from disclosure." This authorization did not include "trade secret information prohibited from disclosure by statute." (Appendix C.)

After consideration of important issues for this study, Panel members reviewed information submitted in response to both an announcement published in the Commerce Business Daily and to individual solicitation. Information was provided in written submissions and by individual closed-session presentation to the Panel. The extensive discussion and careful deliberation that followed resulted in the observations, conclusions, and recommendations presented in this report.

Although the Nation's blood supply is safer than it has ever been, the potential to improve logistical efficiency in supplementation of oxygen carrying capacity, reduce or eliminate risk of disease transmission, and reduce cost has far reaching beneficial implications. The Panel believes that a safe, effective, and practical red cell substitute is feasible, and this difficult goal should be actively pursued until achieved. To do this most effectively, a National commitment is required. Greater understanding of basic mechanisms and toxicities is needed. Lack of this knowledge will likely preclude availability of an approved product in the near future.

The needs of the military for a red cell substitute were considered in comparison to requirements for a product for civilian use. While the military may have greater concerns for logistical considerations (e.g. weight, volume, storage temperature), these concerns are relative. When used for the same clinical indication, there are no unique military requirements for an "ideal" substitute that differ significantly from an "ideal" product for civilian use. Even when an acceptable substitute is available, a blood banking system will still be needed to supply other elements of whole blood required for specific purposes other than carrying oxygen.

All technologies reviewed seek to approach the exquisite balance of structure and function found in the normal red cell. Hemoglobin free in the bloodstream (outside the red cell) carries oxygen, but it rapidly breaks down into its subunits and exerts many adverse effects. Some technologies are directed at overcoming problems associated with free hemoglobin. An example is chemical modification of human or non-human (mostly bovine) hemoglobin in an effort to retain the beneficial oxygen carrying properties of the free hemoglobin while minimizing deleterious effects. Other technologies use genetic engineering for production and modification of hemoglobin generated in bacteria, yeast, or other animal species. Hemoglobins may also be encapsulated in artificial cell membranes to simulate the red cell. A technology not based on hemoglobin involves the use of emulsions of perfluorocarbon compounds which carry oxygen in the blood dissolved (not bound) in the emulsion.

Industry has built upon information generated by previous publicly funded research in the field. Industry is developing facilities to produce purified products, and testing in animals and preliminary tests in humans are in progress. Much proprietary research has been conducted by industry, but because of its proprietary nature, the information often does not benefit from peer-review and scrutiny in the scientific literature. Furthermore, it is not often made available to expand the scientific base of knowledge in the field.

In early clinical trials in humans (Phase I) reported to the FDA, small doses of product were given to normal healthy volunteers. Phase I testing using soluble hemoglobins and perfluorocarbon emulsions has been done. Results have shown some adverse effects for each of the products tested. No product has been allowed to progress to Phase II testing. Surprisingly, adverse reactions reported in Phase I trials in humans were not predicted by results of prior animal studies. The complexity of problems associated with development of a red cell substitute will likely preclude its availability for several years.

The field is not sufficiently advanced to identify a leading technology, and progress is stalled. Problems are not likely to be solved in the near future without a National commitment to developing a red cell substitute. This red cell substitute program should be funded for a period of at least five years (beginning in FY 93) at a level of \$50 million per year. This funding should not be to the exclusion of other blood related research. Funding for product development and manufacturing should continue to come from the private sector.

The Panel recommends that the Congress direct the Department of Defense and National Institutes of Health, with the active support of the Food and Drug Administration, to work together to jointly establish and execute a program of excellence based on peer-review and scientific merit. Critical obstacles in development of a red cell substitute must be addressed and overcome. This effort should foster an increase in the number of investigators in the field. It is essential that all information generated by this program be disseminated in the scientific literature in a timely manner, or otherwise remain in the public domain.

Successful development of an approved red cell substitute will likely have many beneficial implications beyond the scope of those currently envisioned.