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Oxygen carriers as alternatives to red blood cell transfusion

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INTRODUCTION

Alternatives to red blood cell transfusion have been long-anticipated and sought-after developments in biotechnology and medicine. It is generally understood that a manufactured substance cannot carry out the numerous and complex functions of blood, but terms such as "artificial blood" or "blood substitutes" remain popular with the media and the public. Research efforts have been directed toward products that perform the oxygen-carrying and other transport functions of red blood cells. These products are referred to as oxygen carriers (OCs) or oxygen therapeutics (OTs).

This article will provide historical and clinical background and updates on the status of ongoing clinical protocols [1-3].

Red blood cell transfusion and other aspects of tissue oxygen delivery are discussed separately.

- Indications for transfusion (newborns) – (See "[Red blood cell transfusions in the newborn](#)".)
- Indications for transfusion (infants and children) – (See "[Red blood cell transfusion in infants and children: Indications](#)".)
- Indications for transfusion (adults) – (See "[Indications and hemoglobin thresholds for red blood cell transfusion in the adult](#)".)
- Indications for transfusion (critically ill) – (See "[Use of blood products in the critically ill](#)" and "[Massive blood transfusion](#)".)
- Normal hemoglobin function – (See "[Structure and function of normal hemoglobins](#)".)

- Oxygen delivery – (See ["Oxygen delivery and consumption"](#) and ["Measures of oxygenation and mechanisms of hypoxemia"](#).)

HISTORY OF OC DEVELOPMENT

Attempts to develop substances that could replace blood date to the 17th century and continued into the mid-1800s when hemoglobin solutions were infused experimentally into humans [4,5]. These infusions resulted in significant morbidity and mortality, mostly from the nephrotoxic effects of free hemoglobin and red blood cell stroma [6]. This discouraged further activity of consequence, but research was renewed when the wars of the 20th century raised awareness that an easily stored, transportable, and abundant OC was an important medical therapeutic.

The human immunodeficiency virus (HIV) epidemic was a watershed phenomenon that catalyzed early modern research in the 1980s and propelled the search for such a product to then-peak levels in the 1990s and 2000s. Additional factors that contributed to renewed interest included the potential contamination of blood by other pathogens, immunologic complications of allogeneic transfusion, the need for pretransfusion compatibility testing such as crossmatching, and special storage requirements. (See ["Blood donor screening: Laboratory testing"](#) and ["Risk of HIV from blood transfusion"](#) and ["Immunologic transfusion reactions"](#) and ["Leukoreduction to prevent complications of blood transfusion", section on 'Immunosuppression'](#).)

While efforts to develop OCs were underway, infectious risks of transfusion from known pathogens continued to decline due to improvements in blood donor screening and testing. This reduction in infectious risk, as well as simultaneous efforts to develop pathogen inactivation technologies, may have decreased a sense of urgency for OCs. However, in a survey sponsored by a biotechnology company specializing in blood pathogen inactivation, at least 84 percent of 502 Americans surveyed essentially still perceived blood as a threat to patient safety [7]. A public health problem that may continue to drive development of these products is the challenge of persistent blood shortages in the United States and globally. It is projected that by the year 2030 there could be a shortfall of 4 million units annually in the United States [8,9]. The worldwide need is for over 200 million units per year in countries that lack testing and storage capabilities to support an allogeneic blood supply [10].

At the turn of the 21st century, there was optimism that rapidly advancing technology would imminently lead to OCs for use in a variety of clinical settings. Several products advanced to phase III clinical trials, but reports of adverse events and regulatory concerns about safety led

to trial terminations. Allegations that some companies may have misled investors or withheld outcome results and the inability to obtain regulatory approval and sustain investor support also resulted in the withdrawal of products [11,12]. In 2009, the two then-remaining companies filed for bankruptcy and discontinued manufacturing activities.

In spite of these setbacks, a pressing need for oxygen therapeutics remains, and work continues in the field. Although no OCs are currently licensed by the US Food and Drug Administration (FDA) for use in the United States, new insights into the basic biology and physiology of hemoglobin and gas transport systems are informing the development of products and potential applications through FDA-approved protocols.

CHARACTERISTICS OF AN IDEAL OC

An ideal substance for carrying (and delivering) oxygen would have the following characteristics:

- Rapid availability
- Effective oxygen-carrying capacity and provision of volume expansion
- Appropriate physiologic interaction with nitric oxide (NO)
- Sterility (absence of pathogens) to the extent possible
- Minimal side effects
- Viability over a range of storage temperatures
- Extended shelf life
- Universal compatibility and elimination of crossmatching
- Cost effectiveness
- Adequate inventory levels

An additional benefit would be the ability of chemically or genetically modified products to work in special and specific clinical situations, mentioned below.

CATEGORIES OF OXYGEN CARRIERS

Historically, two major categories of OC have been developed:

- Hemoglobin-based oxygen carriers (HBOCs)
- Perfluorocarbons (PFCs)

Hemoglobin-based oxygen carriers — Hemoglobin for HBOCs has been derived from two mammalian sources: bovine and human blood, the latter primarily from outdated red blood cell units. Hemoglobin is first separated from the red blood cell stroma through ultrafiltration and purification [13].

Mammalian-derived hemoglobin can then be chemically modified by polymerization, crosslinking, pyridoxylation, and/or pegylation (addition of polyethylene glycol [PEG] molecules), which prevent the dissociation of hemoglobin from its native four-chain configuration into its basic alpha-beta dimers [14]. A product in which carbon monoxide molecules have been added to prevent nitric oxide (NO) binding by hemoglobin may reduce vasoconstriction [15]; this might also reduce the vasoconstriction that is a noted complication of sickle cell disease. (See '[HBOC-associated side effects](#)' below and "[Mechanisms of vaso-occlusion in sickle cell disease](#)".)

More recently, nano- or microparticle delivery platforms to deliver hemoglobin have been developed [16].

- **Polymerization** – Polymerization of some HBOC converts the four-chain hemoglobin moiety into larger two to four hemoglobin molecule-containing polymers [17].
- **Crosslinking** – Crosslinking of alpha chains prevents dissociation of the hemoglobin molecule into alpha-beta dimers, which, with a molecular weight of 34,000, would otherwise be small enough for glomerular filtration, resulting in hemoglobinuria and nephrotoxicity.

Polymerization and crosslinking appeared to have addressed some of the problems associated with unmodified stroma-free hemoglobin. Half-life increased from a few hours to 12 to 48 hours [18]; glomerular filtration decreased, reducing or effectively eliminating nephrotoxicity; and oxygenation was improved as a result of lowered oxygen affinity of some products (eg, P50 as high as 54 mmHg) [14,19,20]. However, trials of one of the crosslinked products were associated with increased mortality; consequently, development of at least one HBOC formulation was terminated [21-23].

- **Microparticle delivery** – Liposome-encapsulated hemoglobin (LEH) seemed to confer advantages such as a longer intravascular half-life and the potential for freeze-dried storage [18]. Significant immunologic reactions, mostly due to interactions with the liposomal membrane, stalled the development of this OC [24-26].

Hemoglobin has also been produced through recombinant technology. This approach showed promise in the early 1990s and involved the use of *E. coli* transfected with human hemoglobin

genes. In animal models, however, vasoconstriction attributed to scavenging of nitric oxide by the recombinant product and elevated amylase and lipase levels were observed, suggesting decreased pancreatic perfusion [27-29]. Efforts on this product were abandoned in 2003.

Perfluorocarbons — Perfluorocarbon (PFC) products were among the earliest of the 20th Century OCs. A 1960s-era magazine depicted a memorable photograph of a breathing rodent submerged in a beaker of PFC, introducing a brave new science to the public [30].

PFCs are inert compounds in which fluorine replaces hydrogen atoms. Water insolubility necessitates emulsification, for which egg yolk phospholipid was used in trials in dogs [31]. PFCs have a plasma half-life of approximately 12 hours. They were deemed stable for up to two years under refrigeration at approximately 4°C [13].

Unlike HBOCs, PFCs do not carry gases, but because of their decreased surface tension and intramolecular action, they act as highly efficient solvents and have the capability of absorbing significant amounts of gas [13,18,31]. Their oxygen-carrying capacity is linearly related to the PO₂, and patients receiving these agents could require high concentrations of supplemental oxygen.

- In 1989 the FDA approved the PFC Fluosol for perfusion of ischemic tissues in the setting of percutaneous transluminal coronary angioplasty. This was the first such product ever licensed [32]. Fluosol was withdrawn from the market in 1994 due to lack of commercial success.
- Results of a randomized trial from Europe of perflubron emulsion in non-cardiac patients suggested that, when used in conjunction with acute normovolemic hemodilution, there were slightly decreased requirements for allogeneic blood versus the control group [33].
- A trial of the PFC Oxybyte to improve oxygen delivery in traumatic brain injury was halted in 2014 due to low enrollment [34,35].

PFC clinical trials are not actively taking place in the United States (US). This does not preclude future investigations, as at least one agent, Vidophor (formerly Perftoran), which is used outside the US, may be awaiting trials [36].

POTENTIAL USES FOR OCs

The clinical areas for which OCs were originally considered to have the greatest potential were cardiovascular elective surgery and hemorrhagic shock related to trauma and acute blood loss.

Surgery — In the surgical setting, the goal of clinical trials had been to postpone, reduce, or eliminate the need for allogeneic blood transfusions, especially in cardiovascular procedures (including priming of the bypass pump) and situations in which bleeding could exceed anticipated levels [13,37]. In some studies, patients who received hemoglobin-based oxygen carriers (HBOCs) for cardiac, aortic, or emergency surgery required substantially fewer allogeneic red blood cell (RBC) units compared with controls [38-40].

Hemorrhagic shock — Because animal data suggested that the outcome of hemorrhagic shock correlated with tissue hypoxia, it was hypothesized that in humans, acellular oxygen-carrying resuscitation fluids could improve outcomes related to hemorrhagic shock in trauma or acute blood loss when blood was not immediately available [41,42].

In preclinical studies, hemoglobin solutions and perfluorochemical (PFC) compounds were used to resuscitate animals with severe hemorrhagic shock. These compounds appeared to result in more rapid restoration of normal tissue metabolism and improved survival over crystalloid or colloid solutions [43-45].

However, the apparently beneficial effects of OCs observed in animals were not replicated in at least two human trauma trials.

- In a 1999 trial, 112 patients with traumatic hemorrhagic shock and unstable vital signs were randomly assigned to receive either diaspirin crosslinked hemoglobin solution or [saline](#) [22]. Patients who received the OC had significantly higher mortality at 2 and 28 days (46 versus 17 percent at 28 days). The mechanism by which diaspirin crosslinked hemoglobin might have worsened outcomes is unclear but may have been related to its actions as a nitric oxide scavenger and/or its vasoconstrictive effects, which may have accelerated the rate of hemorrhage [46]. (See '[HBOC-associated side effects](#)' below.)
- In a 2009 multicenter trial, 714 patients with hypotensive injuries (systolic blood pressure ≤ 90 mmHg) were randomly assigned to receive a human polymerized hemoglobin preparation or crystalloid. Subgroup analysis showed that the experimental OC was associated with significantly higher 30-day mortality and a higher incidence of coagulopathy and myocardial infarction in blunt trauma patients.

Concerns have frequently been raised about whether participants in trauma studies would be able to provide informed consent to receive an OC [47-49]. These ethical considerations may continue to inform the design of trials for trauma and other hemorrhaging patients, including those in pre-hospital treatment settings, who may not be able to provide informed consent prior to infusion.

Oxygen therapeutics as bridging agents in acute anemia — Although adverse events and other challenges have resulted in fewer OC clinical trials for trauma patients, case reports have suggested that OCs could potentially provide a stabilizing or interim benefit to patients with acute anemia, thus serving as oxygen-bridging agents.

Such clinical situations may involve patients for whom blood is not an option (BNAO) because of religious convictions, such as Jehovah's Witnesses, who may accept an OC [50-58], and patients for whom compatible blood is not available. The following represent such clinical situations:

- An exsanguinating patient with hemolytic anemia likely was saved by the infusion of an HBOC [18,59].
- A patient with sickle cell disease and acute chest syndrome, delayed hemolytic transfusion reaction, and hyperhemolysis attributed to two high-frequency antigens (anti-N and anti-Do^a) was treated with multiple modalities that included [eculizumab](#), steroids, intravenous iron, intravenous [immune globulin](#) (IVIG), and vitamin B12; the patient also received HBOC-201, which was believed to possibly play a lifesaving role [60].
- Other reports have described Jehovah's Witnesses who were successfully managed by treatment with a PFC or an HBOC in settings such as trauma, severe postoperative anemia, acute chest syndrome, abruptio placenta, or chemotherapy-induced anemia [52,54-57,61,62]. (See "[The approach to the patient who declines blood transfusion](#)".)

Further discussion regarding the use of OCs in these settings is discussed below and in a separate topic review. (See '[Resources and processes for obtaining OCs in the United States](#)' below and "[The approach to the patient who declines blood transfusion](#)", section on '[Improve oxygen delivery](#)'.)

Other potential applications — The size of HBOCs and PFCs compared with RBCs (<0.1 versus 7 microns, respectively) could theoretically allow OCs to facilitate oxygen transport to poorly oxygenated areas that are not accessible to RBCs [13]. The potential to reach these tissues led to optimism that such products could be used in vaso-occlusive episodes such as stroke and acute pain events associated with sickle cell disease [63,64]. The availability of such products could be especially important in sickle cell disease if compatible blood is not available in a timely way for a patient with multiple or rare RBC alloantibodies [65]. It has also been proposed that the radiation- and chemo-sensitivity of some tumors could be enhanced by OCs, one of which had been under development for this purpose [66].

The relatively brief intravascular activity of OC makes it unlikely that these agents will replace RBC transfusions for patients with long-term or chronic transfusion needs.

RESOURCES AND PROCESSES FOR OBTAINING OCs IN THE UNITED STATES

Feasibility of obtaining OCs — If an unlicensed OC is available under a US Food and Drug Administration (FDA) Expanded Access protocol, it may be possible obtain units for life-threatening anemia in some patient populations such as those for whom blood is not an option (BNAO), as demonstrated by the following examples:

- **Polymerized bovine hemoglobin** – A 2010 case report described a Jehovah's Witness (JW) with acute lymphoblastic leukemia (ALL) who was successfully treated for life-threatening anemia with 15 units of a hemoglobin-based oxygen carrier (HBOC) consisting of polymerized bovine hemoglobin (HBOC-201; Hemopure) [67].

A 2013 case report described the successful two-unit transfusion of HBOC-201 for a 19-year-old JW with warm autoimmune hemolytic anemia (AIHA) and a hemoglobin of 2.8 g/dL [68].

A 2018 case report described successful use of an HBOC in three individuals with sickle cell disease, two of whom could not receive blood because they were JWs and one for whom compatible blood could not be found due to the presence of alloantibodies [69]; all had nadir hemoglobin levels <6 g/dL (two were <4 g/dL). Infusion of the OC enabled sufficient recovery and discharge from the hospital. Two of the individuals developed methemoglobinemia requiring treatment with ascorbic acid and two experienced transient hypertension.

A 2020 retrospective observational study reported on 10 acutely anemic patients for whom blood was not an option, who between 2014 to 2017 received 10 to 27 units of HBOC-201 over 5 to 14 days. Most patients declined blood because of religious convictions. All survived, but the authors cautioned that this survival rate may not be assumed in all situations and could depend on underlying patient conditions. The main adverse effects were elevation in blood pressure and methemoglobinemia, for which management approaches were described. Transient adverse events included gastrointestinal effects, volume overload, liver enzyme elevations, and decreases in oxygen saturation by pulse oximetry. This paper is important as it described larger cumulative doses of HBOC-201 and longer treatment periods than previously reported. It also demonstrated the role of expanded access in obtaining products for patients with severe anemia [70].

- **Pegylated bovine carboxyhemoglobin** – A 2018 case report described a 42-year-old JW with a lymphoproliferative disorder and gastrointestinal bleeding with a hemoglobin of 3.1 g/dL who was successfully treated over seven days with 6 units of a bovine pegylated

carboxyhemoglobin (PCHB, SANGUINATE) [71]. These infusions bridged the patient to interventions such as endoscopy and interventional radiology coil embolization.

Other case reports include the successful use of this product in JW patients who underwent liver transplant, cystoprostatectomy and nephrectomy, and gastric bleeding related to nonsteroidal antiinflammatory drug use [72-74].

These and other studies suggest an encouraging potential role for OCs as oxygen-bridging agents for patients with life-threatening anemia. (See '[Hemoglobin-based oxygen carriers](#)' above and '[The approach to the patient who declines blood transfusion](#)').

Process for obtaining OCs — The [ClinicalTrials.gov](#) site of the US National Institutes of Health (NIH) is an important resource for identifying clinical trials. A standardized format provides the protocol title and category, product name, protocol identifier and status, trial description, inclusion and exclusion criteria, contact information for the manufacturer or principle investigator, and other relevant other information. For OCs, appropriate terms to search include "oxygen carriers," "oxygen therapeutics," "HBOC," "perfluorocarbons," "PFC," and "blood substitutes."

The process for obtaining a product under "Expanded Access" (EA; previously referred to as "compassionate use") is as follows [75]:

- Contact the manufacturer – Contact information is usually available in the protocol information at [ClinicalTrials.gov](#).
- Contact the FDA Center for Biologics Evaluation and Research (CBER):
 - Daytime phone number – 800-835-4709.
 - After-hours emergency number – 866-300-4374.

The FDA will work with the manufacturer through an emergency IND (eIND) process.

- Obtain approval from the requesting facility's Institutional Review Board (IRB).

The availability of specific OC products via this process varies, and occasionally no products are available under an EA protocol. The unlicensed OC HBOC-201 (Hemopure), a purified, crosslinked, polymerized, acellular bovine hemoglobin manufactured in the United States, is not approved by the FDA but may be available through FDA-approved EA protocols for special instances of life-threatening anemia in those for whom allogeneic red blood cell transfusion is not an option, per the process described above [76]. EA information for other products is

available via [ClinicalTrials.gov](https://clinicaltrials.gov). If a clinician is familiar with a specific product name, an inquiry can be made regarding whether the named product is accessible through an EA.

ADVERSE EFFECTS

HBOC-associated side effects — The following adverse effects have been proposed:

- **Vasoconstriction** – Vasoconstriction and pressor effects have been described [77-79]. A recognized cause is the scavenging of nitric oxide (NO) by hemoglobin in some OCs [13,80-86]. NO, also called endothelial-derived relaxing factor (EDRF), has vasodilatory properties, and NO scavenging, which decreases its availability to vasculature, can cause systemic vasoconstriction, decreased blood flow, release of proinflammatory mediators, and loss of platelet inactivation, potentially leading to thrombosis in the heart and/or other organs [14,46,87]. To address this problem, a bovine pegylated carboxylated (PCHB) product (SANGUINATE) was "designed to provide a low-level therapeutic release of carbon monoxide that inhibits vasoconstriction" [88,89]. This product is discussed in more detail above. (See '[Hemoglobin-based oxygen carriers](#)' above.)

The role of NO in vascular biology and potential adverse effects of NO scavenging are discussed in more detail separately. (See "[Structure and function of normal hemoglobins](#)", [section on 'Nitric oxide transport'](#) and "[Inhaled nitric oxide in adults: Biology and indications for use](#)", [section on 'Biology and pharmacokinetics'](#).)

Other proposed mechanisms of vasoconstriction with HBOCs include autoregulatory vasoconstrictive reflex of excess tissue oxygen concentrations, the oxidation properties of hemoglobin as it degrades, an adrenergic effect caused by the direct action of hemoglobin on peripheral nerves, and carrier interaction with endothelin, a regulator of vascular tone [90].

- **Hemostatic effects** – Studies in rabbits showed an increased hemostatic effect of HBOC, perhaps related to reversal of the inhibitory effect of NO on platelet adhesion and aggregation [91,92].
- **GI symptoms** – Reported gastrointestinal (GI) side effects have included nausea, vomiting, diarrhea, dysphagia, bloating, and other symptoms. Symptoms have been reported as mild to moderate and usually not requiring treatment. Lack of availability of NO in GI tissues has been a proposed cause [93].

- **Immunomodulatory effects** – Immunosuppression leading to increased risk of infection was reported in animals, and surveillance for this effect may be warranted in human trials [94,95].
- **Changes in laboratory values** – The adverse effect of HBOCs on laboratory tests has been attributed to the higher plasma hemoglobin concentrations that can occur with infusion of an HBOC. Tests that have yielded inaccurate results in the presence of HBOCs include liver enzymes, bilirubin, amylase, and others, including optical assays for coagulation times [93,96]. In a 2018 single case study of a patient transfused with HBOC-201, four common chemistry analyzers demonstrated cross-platform variability in multiple assays [74,97]. In one publication, laboratory tests that were not affected by the presence of HBOCs have included electrolytes, glucose, blood gases, creatinine (enzymatic methods), and PT and aPTT (mechanical methods) [96].
- **Adverse effects on survival** – Findings from a seminal meta-analysis that assessed the safety of HBOCs in a total of 3711 patients enrolled in 16 trials involving five different hemoglobin-based OC products contributed to the decline of product development [14]:
 - Compared with control groups receiving other treatments (allogeneic blood, crystalloids, colloids), those receiving HBOCs had a statistically significant increase in the risk of death following the use of these agents (risk ratio [RR] 1.30, 95% CI 1.05-1.61).
 - Compared with controls, patients receiving an HBOC had a significantly increased risk of myocardial infarction (RR 2.71, 95% CI 1.67-4.40).
 - Subgroup analysis indicated that these increased risks were not restricted to a particular HBOC preparation or clinical indication (surgery, stroke, or trauma).

An accompanying editorial concluded that, given these findings and the consistency of these results with preclinical evidence of potential toxicity, further trials of HBOCs should not be conducted until it could be shown that these agents were at least as effective in reducing mortality or serious morbidity as the available standards of care [98]. However, HBOCs have subsequently undergone re-assessment, as described below. (See '[History of regulation and licensure](#)' below.)

PFC-associated side effects — The major clinical problems associated with perfluorocarbons (PFCs) were flu-like symptoms attributed to cytokine-mediated effects, and platelet sequestration in the spleen and liver, causing hepatosplenomegaly and lowering of the platelet

count by as much as 40 percent [13]. A comprehensive review of PFCs, clinical trials, and adverse effects is available [99].

While this particular comprehensive review focused on most commonly reported effects, other less common effects have also been described [16,36,70]. An industry-sponsored publication from South Africa also summarizes a large experience with PFCs in over 1700 patients [100].

The requesting physician should carefully review information on adverse effects and recommended treatments provided in the manufacturer's product information or Investigator Brochure.

CHALLENGES

The decreased sense of urgency for OCs (see '[History of OC development](#)' above) and concerns about adverse effects and short intravascular life have hindered regulatory approval for continued research and clinical applicability. Other issues have included supply, cost, and regulatory requirements, as discussed in the following sections.

Supply — If a human hemoglobin-based oxygen carrier (HBOC) were to receive regulatory approval, it is estimated that 70,000 kg of hemoglobin would be required to replace 20 percent of the United States allogeneic red cell transfusions annually [101]. Limitations on availability, management, and manufacturing of raw materials would present significant challenges.

Two units of red cells are required to produce one therapeutic HBOC dose as formulated. However, the expiration rate of human blood donated by volunteers is extremely low, making this a truly scarce resource. Furthermore, it is not known whether volunteer blood donors would support the raw materials needs of a commercial biotechnology enterprise. A human hemoglobin-based product, Hemospan (MP40X), would have faced these challenges, but the manufacturer ceased operations due to several factors, including at least one clinical trial that showed higher rates of adverse events than hydroxyethyl starch [102].

Animal-derived (eg, bovine) hemoglobin requires intensive management of large herds. At a minimum, animal testing and careful herd management is necessary to address possible regulatory or public concerns about contagion from source animals. This concern was compounded by reports that allogeneic transfusion was the likely cause of human-to-human transmission of variant Creutzfeldt-Jakob disease (the human variant of bovine spongiform encephalopathy) [103,104]. (See "[Blood donor screening: Medical history](#)", section on '[Variant Creutzfeldt-Jakob disease](#)' and "[Variant Creutzfeldt-Jakob disease](#)", section on '[Bovine spongiform encephalopathy](#)'.)

Cost — Manufacturers of HBOCs are prohibited by federal regulations to discuss pricing information for products under development or in clinical trials. Given other challenges facing OC manufacturers, the market potential may be limited unless the price of a red cell unit-equivalent eventually approaches that of an allogeneic red cell unit, which is approximately \$300 to \$400 USD, including crossmatching and other costs. Two earlier HBOC price estimates ranged from \$400 to \$800 USD per unit [[105,106](#)].

History of regulation and licensure — Like other pharmaceuticals and biologics, OCs must meet FDA safety and efficacy requirements to obtain approval.

Since 1991, the FDA has been communicating safety and efficacy expectations to the biotechnology community [[107,108](#)]. In late 1999, the agency conducted a workshop with the National Institutes of Health that comprehensively addressed possible clinical uses for OCs [[109](#)]. These documents provide important insights into the thinking and expectations of the FDA at that time.

Optimism in the early 2000s about near-term approval of OCs was dampened by the discontinuation of research into the use of crosslinked hemoglobin after a trial of a diaspirin crosslinked hemoglobin OC (HemAssist) showed a higher mortality rate in recipients of the OC versus controls [[22,110](#)]. Efforts to advance recombinant product trials were discontinued because of reported adverse effects [[110](#)]. Following the outcome of the HemeAssist trial, the FDA expanded the clinical testing requirements for all similar products, causing a deceleration in trial approval [[111,112](#)]. (See '[Hemorrhagic shock](#)' above.)

In 2006, the National Heart, Lung, and Blood Institute (NHLBI) convened a workshop to evaluate scientific issues that were critical to developing HBOCs [[113](#)]. Concerns about adverse cardiovascular events resulted in the development of recommendations for basic research that would be critical for developing safer products.

In 2017, a plan to resume HBOC development and evaluate new clinical trial protocols was discussed at a joint meeting of the FDA, NIH, and Department of Defense. Possible outcomes may be an increase in oxygen therapeutics research and development; approval of new clinical trials may occur at a faster pace than that observed in the past several years [[100](#)].

OTHER PRODUCTS UNDER DEVELOPMENT

In vitro RBC production or modification

Cell culture — Advances in cellular engineering have made it possible to culture red blood cells (RBCs) *in vitro* from hematopoietic progenitor cells, which may represent an exciting, viable approach to meeting global red blood cell transfusion needs. Potential sources of hematopoietic progenitor cells include umbilical cord blood, adult peripheral blood, multipotent stem cells, and immortalized adult erythroid progenitor cells [114].

In a proof of principle study in mice and a human volunteer, transfused RBCs cultured from autologous CD34 cells demonstrated attributes consistent with endogenous RBCs such as oxygen binding and release, deformability, enzyme content, expression of ABO antigens, and viability [115]. This is an exciting step, but considerable challenges to the large-scale production of RBCs for therapeutic transfusion purposes exist, including significant biologic, regulatory, funding, and logistic issues.

Elimination of blood group antigens — Group O blood can be administered to individuals of any ABO blood type. (See "[Pretransfusion testing for red blood cell transfusion](#)", section on 'ABO and RhD type'.)

Enzymatic conversion of type A, B, and AB RBCs to group O has been achieved *in vitro* via the use of exoglycosidases derived from bacterial sources [116]. This enzymatic conversion (ECO) technique, if proven to be safe and effective, has the potential to simplify transfusion by eliminating the risk for ABO-incompatible transfusion errors and creating a more universal RBC inventory [117].

Other emerging products — Additional oxygen carriers that are under development but at this time are not in clinical and are not listed in ClinicalTrials.gov as having EA availability include the following:

- **ErythroMER** – ErythroMER is described as an encapsulated hemoglobin-based "deformable cross-linked polymeric nanoparticle" [118,119].
- **HemoACT** – HemoACT is a human hemoglobin linked with human albumin [120].
- **Oxyvita** – Oxyvita is a liposome-encapsulated, polymerized bovine hemoglobin in which increased polymerization creates a large macromolecule [121,122].

SUMMARY AND RECOMMENDATIONS

- An ideal substance for carrying and delivering oxygen would have similar properties to red blood cells (RBCs), as well as a long shelf life, cost effectiveness, and minimal side effects. Two major categories of oxygen carriers (OCs) that have been developed and have

undergone evaluation are hemoglobin-based carriers (HBOCs) and perfluorocarbons (PFCs). Research on PFCs appears to be primarily focused on diagnostic applications and other clinical uses rather than as an alternative to RBC transfusion. (See '[Characteristics of an ideal OC](#)' above and '[Categories of oxygen carriers](#)' above.)

- No OCs are licensed by the FDA for routine use in the United States. The clinical areas for which OCs originally appeared to have potential were hemorrhagic shock related to trauma with acute blood loss and elective cardiac surgery. However, the focus has shifted to the use of HBOCs as oxygen-bridging agents for situations in which blood is not an option (BNAO) or blood is unavailable due to incompatibility. [ClinicalTrials.gov](#) and several FDA sources are potentially time- or life-preserving resources. (See '[Potential uses for OCs](#)' above and '[Resources and processes for obtaining OCs in the United States](#)' above.)
- The major side effects reported for HBOCs have included, but are not limited to, vasoactivity and gastrointestinal symptoms. Supply and cost issues also may present challenges to future use. (See '[Adverse effects](#)' above and '[Challenges](#)' above.)
- New ideas for HBOCs and methods for generating or modifying RBCs in vitro are being cautiously pursued. (See '[Other products under development](#)' above.)

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