Chapter 9
Regulatory Framework for Hemoglobin-Based Oxygen Carrier Trials

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9.1 Introduction

Oxygen therapeutics (OT) consist of hemoglobin-based oxygen carriers (HBOCs) and fluorocarbons. They have been developed to deliver oxygen (O_2) to tissues, mainly for treatment of shock due to blood loss. These products are being developed in order to treat blood loss when red blood cells are not available, as may occur on the battlefield or in civilian life when trauma occurs.

Investigational HBOCs have been shown in clinical trials to be associated with serious adverse effects including stroke, myocardial infarction, renal failure and death, and none have been approved by the FDA (Chen et al. 2009). As of this writing, FDA has issued a draft guidance addressing the criteria for safety and efficacy evaluation of oxygen therapeutics as red blood cell substitutes, but FDA has not issued the final, guidance (Guidance for Industry 2004).

Drug development of such products is not different from other drug products and involves, manufacturing under current Good Manufacturing Practice (GMP) conditions, biochemical characterization, pre-clinical studies, and clinical studies (Guidance for Industry: 2008). The focus of this chapter is on clinical studies that manufacturers may wish to consider for new generation HBOCs, (Guidance for Industry 2004).

The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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9.2 General Approach to Clinical Studies

Clinical trials should be performed according to Good Clinical Practice Guidelines (Guideline for Good Clinical Practice 2002) and follow a certain order that should also be applied to HBOCs under the investigational new drug (IND) provisions. These include Phase 1 safety studies, Phase 2 exploratory, and Phase 3 pivotal trials (21CFR312.21) (Guideline for Good Clinical Practice 2002). One challenge with HBOCs is that they are often intended for subjects in shock who may not be able to give the informed consent required for a clinical trial. Clinical trials with exception from informed consent are subject to specific conditions (21CFR50.24) which are discussed below. Clinical development programs of HBOCs can be complex, particularly if they involve clinical studies in severely injured patients with an exception from informed consent. Therefore, it is strongly advised that sponsors approach the FDA early in the development process to discuss potential study designs, including choice of study population, and other relevant matters.

Manufacturers generally are asked by FDA to perform studies in healthy volunteers and surgical patients before considering studies in the trauma population. This was the approach adopted by several manufacturers in their drug development programs for HBOCs (Jahr et al. 2012).

Prior to conduct of any clinical studies for any drug or biological product, those products are: manufactured under GMP conditions (21CFR 210.2); characterized in terms of purity and sterility; and tested in animals to assess safety and proof of principle for efficacy. Hemoglobin based products are tested for O_2 affinity (P_{50}), cooperativity (Hill co-efficient), and stability (Guidance for Industry 2004; Buehler and Alayash 2008).

An important safety concern for products derived from human or animal blood or tissues relates to preventing transmission of infectious agents. Biologics derived from human or animal tissue are subjected to multi-tiered safety measures including avoidance of contaminated sources, and viral clearance steps (i.e. inactivation and removal). Since HBOCs are derived from human or animal red blood cells or recombinant sources, the latter concern is pertinent. Human donors are screened for risk factors for infectious agents by questionnaires and their blood is tested for certain infectious agents (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095522.htm). Human plasma used to manufacture plasma derivatives is tested by nucleic acid tests (NAT) for several infectious agents, generally on pooled donor specimens. Viral clearance steps are required in the manufacturing of plasma derivatives including HBOCs. Animals are vaccinated against viruses and animal husbandry is optimized to reduce contact with infected animals (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ Guidances/UCM213415.pdf) (ICH Topic 2000). Additionally, any human and bovine source material may involve the risk of transmissible spongiform encephalopathy (TSE) (WHO 2006). Animal selection and other steps are taken to assure that the animals used are healthy and that the source material is removed in a facility that avoids possible cross-contamination

with TSE infectious agents (WHO 2006; Guidance for Industry 2010). Once a judgment can be made that a product is reasonably safe, based on its characterization and non-clinical data, it may be given to humans (21CFR312).

HBOCs have been shown to interfere with many standard clinical laboratory assays used in monitoring for patient safety. In vitro testing to determine to what extent a "correction factor" is needed, to account for this interference is usually completed before Phase 1 trials can begin (Kazmierczak et al. 1998).

Previous trials with HBOCs revealed serious adverse events in patients undergoing surgery or bleeding as a result of trauma (Guideline for Good Clinical Practice 2002). These have included stroke, myocardial infarction and death. These events were hypothesized as being due to binding to NO and causing ischemia due to vasoconstriction, and to endothelial damage due to release of heme and reactive oxygen substances (Buehler and Alayash 2008). These observations may influence the development of new HBOCs and may need to be considered in future human trials with HBOCs. For example, in order to reduce toxicity, a sponsor may seek to modify a new HBOC product or to co-administer another agent to demonstrate improved safety. Pre-clinical studies are typically performed in accordance with ICH S6 guidance (ICH 1997). Animals studies are important to evaluate a dose range so that "no observable adverse event levels (NOAELs)" can be defined (ICH 1997; ICH Topic E 8 1998). The NOAELs can then be utilized to determine a reasonable margin of safety for the initial dose in humans [21CFR312.23(a)(8)(ii)098].

9.3 Phase 1 Studies

Protocols for phase 1 studies [21CFR312.23(a)(6)(i)] are typically designed to establish the safety profile of the product in healthy volunteers (Guidance for Industry 2008; Guideline for Good Clinical Practice 2002). In the past, manufacturers have conducted studies that included a control group receiving an approved crystalloid or colloid. (Guidance for Industry 2008; Guideline for Good Clinical Practice 2002) FDA regulations require that subjects in a clinical trial should not be exposed to a product unless adequate safety information is available from non-clinical studies [21CFR312.23(a)(8)(ii)] and provided that unreasonable risk of illness or injury can be ruled out [21CFR312.42(b)(1)(iv), (2)(i)]. This is particularly applicable to healthy volunteers that do not stand to benefit from the trial. If the trial design does not meet FDA requirements, FDA can place the clinical trial on hold [21CFR 312.42(b)(2)(ii)].

Special attention to monitoring of adverse events of the nature seen in previous trials of HBOCs, would be appropriate. In the past trials, there were concerns with failure of multiple organ systems including heart (e.g. EKG, troponin) kidneys (e.g. creatinine and GFR), brain (e.g. neurological function), lungs (e.g. pO_2), and gastrointestinal (e.g. amylase and GI distress) (Guideline for Good Clinical Practice 2002; ICH Topic E 8 1998; Buehler et al. 2010).

In most studies investigators proceed with caution with a gradual dose escalation, i.e. starting with low doses and slowly increasing doses to define safe doses for later stage trials (Guideline for Good Clinical Practice 2002; Jahr et al. 2012). There are two approaches to dosing with large volume pharmaceutical like HBOCs, i.e. top-load (i.e. addition to existing blood volume) or exchange transfusion (removing blood while adding HBOC). For indications where large volumes of HBOC will be administered clinically, exchange transfusion approaches to dosing may be considered appropriate. The colloid osmotic effect and viscosity of certain HBOC solutions may add to the concern of fluid overload with these products in hemodiluted subjects, thus hemodynamic parameters should be monitored to avoid fluid overload (Xavier Monnet and Jean-Louis Teboul 2010).

The pace of enrollment will also depend on safety concerns. One subject at a time or several could be enrolled and observed before the next subject or group is exposed to the next highest dose. Again, depending on safety concerns, stopping rules may be required to avoid exposing additional individuals if the product is associated with serious adverse events (Guideline for Good Clinical Practice 2002; ICH 1997).

If the outcome of the phase 1 studies is satisfactory, i.e. no serious adverse reactions are observed, then phase 2 trials can proceed. Alternatively, if the benefit: risk calculation is favorable despite adverse events, then the product may be studied further (Guideline for Good Clinical Practice 2002; ICH 1997).

9.4 Phase 2 Studies

In general, phase 2 trials [21CFR312.23(6)(ii)] are performed on the target population to explore dosage, endpoints, and to obtain additional safety data.

With HBOCs evaluation, this is complicated by the fact that the target population usually identified is severe bleeding during trauma. Such subjects are often unable to provide informed consent for participation in a clinical study because they are in a life-threatening situation necessitating prompt medical intervention and time is insufficient to obtain the consent from legally authorized representatives (LAR). Recognizing the need to permit the study of safety and effectiveness of potential treatments for life-threatening emergencies to improve patient outcomes, FDA issued regulations that allow for a narrow exception from informed consent requirements for emergency research under 21 CFR 50.24. Trials performed with exception to informed consent raise additional regulatory issues that need to be addressed, including: (i) evidence that the product has a potential for direct benefit to study subjects and that current treatments are unsatisfactory or unproven; (ii) adequate public disclosure and community consultation; (iii) appropriate procedural steps to ensure that subjects' family members or LAR are informed of research enrollment; (iv) inability to identify prospectively individuals likely to become eligible to participate, and (v) collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention.

A number of Phase 2 trials for HBOCs intended for severe bleeding in trauma were actually performed in surgical patients (Guideline for Good Clinical Practice 2002), partly because 21 CFR 50.24 regulations do not allow use of the exception from informed consent provisions if the clinical study could practicably be carried out without invoking the exception for emergency research. In previous trials, there were also difficulties associated with conducting the trials with the exception from informed consent (Guideline for Good Clinical Practice 2002). The outcomes were compared to patients receiving blood (Guideline for Good Clinical Practice 2002).

There are advantages to clinical trials with surgical rather than trauma patients. Elective surgery allows for a controlled environment with more stable patients, so that subjects can be carefully monitored. Attribution of adverse effects to the product is more easily assessed than in situations with unstable patients. Elective surgery allows patients to provide informed consent (discussed below) unlike trials in trauma patients where exception from informed consent is a complicating factor. In the past, clinical trials in surgical patients have been designed as randomized trials with HBOC in the test arm and red blood cells as the control arm (Guideline for Good Clinical Practice 2002; Jahr et al. 2012). The primary endpoint was mortality. Secondary endpoints that have been used include morbidity, avoidance of transfusions, and length of hospital stay (Guidance for Industry 2008; Guideline for Good Clinical Practice 2002). The primary endpoint of mortality has the advantage of being most objective and definitive (Guidance for Industry 2008). Statistical plans in the past have included a non-inferiority design comparing HBOCs to red blood cells with mortality as the primary endpoint (Jahr et al. 2012). The implicit objective of such studies was to demonstrate indirectly the superiority of trauma resuscitation with an HBOC compared with colloid or crystalloid, while recognizing the infeasibility to randomize patients to an asanguinous control when blood products are available.

Phase 2 trials are exploratory in nature and may provide sufficient information to allow for the design of pivotal trials. The objectives of Phase 2 trials include: (i) determining optimal dosing by investigating different doses with different rates of delivery; (ii) establishing which primary and secondary endpoints to use in the pivotal trial; and (iii) expanding the safety database in different patient (e.g. different surgery indicated) groups [21CFR312.23(ii)](11, 12).

If satisfactory results are obtained in Phase 2 surgical trials, the next step could be a Phase 2 trial in trauma patients (ICH 1997; ICH Topic E 8 1998). The value of a Phase 2 trial in trauma before embarking on a pivotal trial, would be not only to further determine dosage, establish endpoints, and investigate the safety database in the target population, but also to explore the criteria for identifying subjects that may benefit from the treatment. This could involve use of a scoring system to determine inclusion and exclusion criteria (Yücel et al. 2006).

A Phase 2 trauma trial could be conducted in the ER and thus subjects could be assessed and monitored under more controlled conditions than in a pre-hospital setting. The design may be similar to the surgical trials, in that red blood cells would be the comparator. Ethicists have questioned the appropriateness of a trial in

which use of an HBOC in comparison to colloid or crystalloid was permitted to continue in the ER when blood was available (Chen et al. 2009).

The risks of HBOC administration must be offset by potential benefits. This is where inclusion and exclusion criteria become important. Knowing the risks of dying from trauma for a particular individual, based on a scoring system and supporting database, could greatly facilitate making a reasonable predictive benefit: risk calculation. An example of such a scoring system is the TASH score (Yücel et al. 2006).; whereas the National Trauma Database can be accessed to obtain outcome information (Meredith et al. 2003).

Phase 2 trials are not necessarily powered to show efficacy with statistical significance, but sample sizes should be sufficient for the safety and efficacy data to provide the basis for deciding whether to proceed with a large pivotal trial. If the data show a favorable trend in efficacy and safety supporting a conclusion that there is a reasonable prospect of direct benefit to study subjects, then the sponsor may seek to perform a phase 3 trial, possibly under the exception from informed consent provisions for emergency research as stated in 21CFR50.24.

9.5 Phase 3 Studies

Once Phase 2 trials have shown sufficient safety and efficacy data, it may be reasonable to consider a pivotal Phase 3 trial in trauma. Previously these trials were designed as multicenter randomized controlled trials, powered at 80 % or higher to show superiority over crystalloid, with mortality as the primary endpoint (Guideline for Good Clinical Practice 2002). Blinding of the health care providers to the identity of the HBOC or control fluid may not be possible because of the distinctive color of the HBOC, but those involved in analyzing the data can be blinded.

Prior trauma trials with HBOCs have included an independent data monitoring board (DMB) with well-defined stopping rules and a statistical plan to include interim analyses for safety and futility. A DMB is required for trials performed with exception to informed consent (Guidance for Institutional Review Boards 2011).

9.5.1 Benefit:Risk Calculation

Benefit: Risk calculation plays an important role in decision-making to allow a clinical trial to proceed, but is especially relevant when exception from informed consent is involved (21CFR50.24).

In previous studies, the safety profiles from the Phase1/2 trials have formed a basis for making a benefit:risk assessment. The potential benefit was largely dependent on selection of the target population and knowledge of outcomes with

standard care. This was derived from the literature and databases. The known mortality rate for a particular group of trauma subjects, defined by a scoring system (Yücel et al. 2006; Meredith et al. 2003), was estimated, and the potential reduction in mortality of the investigational HBOC based on animal and human studies (Guidance for Industry 2008; Guideline for Good Clinical Practice 2002) were used to arrive at a benefit:risk calculation to decide whether the trial had a reasonable potential to benefit the subjects.

Secondary efficacy endpoints such as morbidity, length of hospital stay, and the number of red blood cell units transfused, were included in previous trials (Guidance for Industry 2008; Guideline for Good Clinical Practice 2002).

In previous trials, safety was monitored carefully including use of an independent DMB to follow patient safety during progress of the trial (ICH 1997; ICH Topic E 8 1998; Guidance for Institutional Review Boards 2011). The DMB was convened at certain time-points during the trial to determine whether: (i) the trial should continue; (ii) be terminated for futility; or (iii) be terminated because of safety concerns. In addition, stopping rules were in place to stop the trial if adverse events occur at a higher rate than expected as defined a priori (ICH 1997; ICH Topic E 8 1998; Guidance for Institutional Review Boards 2011).

9.6 Conclusion

In conclusion, clinical trials of HBOCs have followed a conventional approach of a series of studies intended to minimize patient risks during product development. In particular, studies in well monitored surgical patients have been required before studies in trauma patients, which generally require exception from informed consent, could proceed. Because clinical development programs of HBOCs can be complex, particularly if they involve clinical studies with the exception from informed consent, FDA input should be sought early on to assure adequacy of the approach to clinical trials.

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