Biocompatible coatings:

Prices for uncoated oxygenator systems list at about $600 and are discounted to as low as $275 to $300 for high volume buyers in adult markets.[1] The premium product, Carmeda's CBAS® total system, lists at about $1,000 and is discounted to as low as $600 for high volume buyers.[2] Carmeda in particular provides extensive training to the perfusion specialists who order and use the equipment in the operating room.[3] There are several biocompatible coatings under development by a variety of companies. In this section only those coatings clinically available on neonatal, pediatric adult blood oxygenators are reviewed. Within this classification, competitors to the Elsius engineered bioactive surface (EBS™):

1. Heparin-bonded coatings:

Carmeda BioActive Surface (CBAS®) - Carmeda AB, a fully owned subsidiary of W.L. Gore & Associates. Located in Vasby, Sweden.

Carmeda is a covalent bonded heparin coating available for license medical device manufacturers for application to pediatric extracorporeal membrane oxygenators. Medtronic applies this surface to their MiniMax Plus pediatric microporous membrane oxygenator. Medtronic effectively owns 100% of the heparin coated pediatric oxygenator market in the United States and approximately 60% of the pediatric market overall.

Strengths with respect to EBS™:

Carmeda is the leader in heparin-based coatings with over 20 years of clinical application and accompanying safety and efficacy data. This clinical credibility presents a potentially significant barrier to entry. Elsius will need to sufficiently excite the end-user such that a trial of the new coating will be undertaken. As discussed above, it is commonplace for a surgical team to insist on familiar and proven products. As a result, the barrier to entry for any new product such as the Elsius coating will be fairly high. The Carmeda coating also has proven itself from a regulatory perspective lowering licensee concerns that the product could complicate or delay their approvals. Based on development to date, there appears to be no technological strengths of the Carmeda coating over Elsius' EBS.

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[1] Alfred Stammers, MSA, SSP in a phone discussion on January 26, 2007.

[2] Ibid.

[3] "Selected Reading: Extensive pre-clinical and clinical experience," Carmeda Web site, http://www.carmeda.com/pages.asp?r_id=2238.

Weaknesses with respect to EBS™:

There are several significant shortcomings to Carmeda's process as applied to pediatric blood oxygenators. Specifically, 1) the required base coat is quite thick and covers membrane pores with a layer impermeable to oxygen and carbon dioxide thus reducing the oxygenator effectiveness; furthermore the Carmeda process may also be wetting and precipitating down in the pores which would be bad for permeance; 2) following drying, sterilization and re-hydration, the heparin's biological activity is diminished due to bonding of negatively and positively charged areas within the heparin and the base layer upon the removal of moisture from the surface; and 3) the coating is not uniform and does not adequately cover all surfaces. Furthermore, Carmeda is an expensive, multi-step process to apply. EBS development specifically considered mass exchange applications during design and hence the coating is thinner and more permeable to oxygen and carbon dioxide than Carmeda. Furthermore, the EBS is projected to reduce costs by 50% per application based on simplifications in the processes and reagents required for application.

BIBA-HEPCOAT[4] - BioInteractions Ltd., located in Reading, England

Medtronic has licensed BIBA-HEPCOAT and markets this as the Trillium coating on their Avecor Affinity adult membrane oxygenator system. The BIBA-HEPCOAT is designed with a polyethylene glycol (PEG) or hydrogel-like space to get the coupled heparin off the surface via a neutral hydrogel spacer. This process has not been shown to have bioactivity as high as Carmeda.

Strengths with respect to EBS™:

Since this coating is claimed to be applicable in a single step, it is possible that it could be more cost effective than the Elsius coating. Medtronic's backing of this coating also provides market credibility and will increase the barrier to entry.

Weaknesses with respect to EBS™:

The patents for this coating do not suggest use of actual heparin, but rather a "heparin monomer" that they produce; the proposed "heparinoid' molecules and concept have never been proven. Data have suggested a low bioactivity and BIBA-HEPCOAT's essentially an anionic surface that may not adhere thrombin.

4 This coating is licensed to Avecor, a unit of Medtronic, and is sold as Trillium Biopassive Surface: BioInteractions Ltd. Web page, http://www.biomateria.com/biointeractions.html.

T2T™ Heparin Biocompatible Surfaces – Medtronic, Inc., Minneapolis, MN

Medtronic's tip-to-tip (T2T) surface is simply a combination of Carmeda and Trillium treated components. The rationale behind this product offering is that the Trillium process complicates coating some components of the CPB circuit; hence, this offers a completely "cannula tip-to-cannula tip" coated CPB circuit. Carmeda and Trillium (BIBA-HEPCOAT) are discussed above separately and not repeated here for brevity. The strengths and weaknesses of the T2T coating with respect to EBS are the same as those for Carmeda and Trillum, which are discussed above and not repeated here for brevity.

GBS Coating - Gish Biomedical, Inc.

The GBS hyaluronan-based heparin coating represents the most recently commercialized product that is clinically available. The coating consists of a hydrophilic biopolymer (hyaluronan) that immobilizes heparin. The base biopolymer irreversibly adsorbs onto the artificial material surfaces. Heparin crosslinks to the base polymer through covalent linkages."[5] This coating is available on the Gish Vision line of adult blood oxygenators.

Strengths with respect to EBS™:

The clinical and commercial credibility of Gish provides the GBS coating with a market advantage over EBS™. While clearly not as dominant as Carmeda or Medtronic, it sill provides a barrier to entry for current customers of the Gish product.

Weaknesses with respect to EBS™:

The GBS coating is based on an adsorption process that best binds to glass and ceramic and poorly to non-polar surfaces. Since this process uses hydrogen bonding as a strong attractive force to surfaces and other molecules the bioactivity of any attached heparin will be lowered and its stability to drying reduced. There is little peer-reviewed evidence that suggest Gish's GBS coating is better than Carmeda. However, since it uses a coating method that results in a thick, impermeable coating, Gish apparently requires a significantly higher surface area than the average in their adult oxygenators (2.45 m^2 versus 2 m^2). Since the Elsius coating has been specifically engineered for optimal performance in a gas exchange application, it is expected that the functional and biocompatible performance will exceed the GBS coating.

[5] S. Gunaydin, K. McCusker, and V. Vijay, "Clinical Performance and Biocompatibility of Novel Hyalouronan Based Heparin Bonded Extracorporeal Circuit," White Paper, on Gish Biomedical Web site http://gishbiomedical.com/pdf/GBSCoatingStudy.pdf?Seg=Cardiovascular%20Solutions&Prod=GBS%20COATING&SubProd=GBS%20COATING.

2. poly-2-methoxyethyl acrylate (PMEA) coatings:

X-Coating, Terumo Corporation

"X Coating™ is an amphiphilic, biopassive coating that reduces protein denaturation and platelet adhesion. This non-heparin coating for the perfusion circuit addresses the goal of heart teams everywhere – to achieve a tip-to-tip coated circuit and improve the biocompatibility of cardiopulmonary bypass."[6] The X-Coating is currently available on the Capiox SX series of membrane oxygenator (neonatal, pediatric, and adult oxygenators).

Strengths with respect to EBS™:

Like Carmeda, Terumo's X-coating is an established product with approximately 10 years of clinical experience and thus has established a firm market position not possessed by the Elsius coating. X-Coating, ™ frequently referred to in scientific literature by its chemical name, PMEA, is Terumo's amphiphilic, biopassive coating. An additional strength – which Terumo actively markets – is that it is not heparin-based, hence there is no potential for heparin-induced thrombocytopenia (HIT). Though this occurs very infrequently, marketing efforts of non-heparin based coatings continue to emphasize this potential complication.

Weaknesses with respect to EBS™:

Unlike the Elsius heparin-based biocompatible coating, the Terumo-X coating has not been designed with mass transfer applications in consideration; hence the gas exchange performance of the coating is not optimized. Though the Terumo X-Coating has been shown to improve platelet number and function, decrease fibrinolysis, and attenuate the inflammatory response in adults, recent studies suggest similar results are not achieved in the pediatric patient.[7] The Terumo X-Coating has been shown to improve platelet number and function, decrease fibrinolysis, and attenuate the inflammatory response in adults but is available only on Terumo's SX series of blood oxygenators. These units use an intraluminal flow path configuration (blood inside of the microporous hollow fiber; sweep gas on the outside) and, as a result, are less efficient than a cross flow configuration. Terumo's RX series of blood oxygenators do possess the more efficient cross-flow configuration preferred by clinicians however the X-coating is not available in this product likely due to process requirements making application impossible. In contrast, EBS is applicable to the preferred cross flow configuration.

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[6] "Biocompatible Coatings," X Coating™, Terumo Cardiovascular Systems Web page, http://www.terumo-cvs.com/about_us/core_competencies/biocompatible_coatings.asp (accessed January 31, 2007).

[7] Kirshbom et al., Journal of Thoracic and Cardiovascular Surgery, 132(3), 675-680, 2006

3. Biomimetic coatings: (Phosphorylcholine)

Smart-X, *Cobe Cardiovascular, Sorin Group*

The Smart-X phosphorylcholine polymer was originally developed by Biocompatibles International plc. (Farnham, Surrey, England) for Dideco - as a licensee – to coat their line of cardiopulmonary equipment. After Sorin s.p.A (Milan, Italy), the parent company of Dideco, acquired Cobe Cardiovascular (Arvada, CO), this coating was renamed the SMART-X and is available on the Cobe Optimin and Lilliput 1 and 2 pediatric oxygenators. Dideco independently markets a KIDS D100 neonatal oxygenator also containing this coating. While phosphorylcholine (PC) shows some reduction in the above mentioned parameters it is not as effective as the Carmeda surface. Furthermore the PC coating is not a phospholipid bilayer as exists on the cell membrane and thus is not really a mimetic surface.

Strengths with respect to EBS™:

The Smart-X coating differs from heparin coatings; Cobe claims the coatings biomimetic characteristics do not disturb the physiological status of the patient's blood and contrasts this to heparin coatings that function by inhibiting formation of fibrin though inhibition of the clotting cascade. As with the Terumo coating, there is no potential for heparin-induced thrombocytopenia (HIT). Though this occurs very infrequently, Elsius has observed that marketing efforts of non-heparin based coatings continue to emphasize this potential complication.

Weaknesses with respect to EBS™:

Like the Terumo-X coating, the Smart-X coating has not been designed with focus on mass transfer performance. Though the Smart-X coating has been shown to improve platelet number and function, decrease fibrinolysis, and attenuate the inflammatory response in adults, recent studies suggest similar results are not achieved in the pediatric patient.[8]

[8] Kirshbom et al., Journal of Thoracic and Cardiovascular Surgery, 132(3), 675-680, 2006